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BIOMATERIALS INNOVATIONS FOR THE FUTURE:
UNVEILING THE TEN MOST CAPTIVATING AREAS FOR ADVANCEMENTS

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Introduction

Owing to the excellent applicability of biomaterials, a rapid and diversified expansion of the biomaterial repertoire has been observed over the last few decades. Biomaterials refer to materials that are designed to interact with biological systems without significant adverse effects. Because of this excellent biocompatibility, biomaterials are commonly engineered to perform therapeutic or diagnostic functions within the body.[1-3]

Biomaterials can be classified as natural or synthetic. Natural materials such as collagen, silk, and cellulose are derived from biological sources, whereas synthetic biomaterials include synthetic polymers, metals, ceramics, and composites. Both natural and synthetic materials can be processed into biomaterials that are useful in modern medicine.[4, 5]

This report employed data from the CAS Content Collection™ and big data analytical approaches. The CAS Content Collection is the largest human-curated and indexed collection of published scientific knowledge, representing a comprehensive resource to access and keep up to date on the world's published scientific literature across disciplines including chemistry, biomedical sciences, engineering, materials science, and many others. Search queries that encompassed the desired topic, biomaterials, were defined by CAS subject matter experts (SMEs). Data pertaining to results from the biomaterials search query was extracted and included the following information: title, abstract, publication year, document type (journal vs patent) and citations. Using Natural Language Toolkit (NLTK) procedures, ~30K phrases were identified using the Python library implementation of NLTK. The emergence of each individual phrase was determined by computing the publication rates and relative growth rates over the last 3 years (2020-2022). In addition, citation graph cohesiveness was also considered during topic ranking. The citation graph cohesiveness was calculated by the number of citations of the publications mentioning a particular phrase divided by the number of publications mentioning that phrase. Those machine-generated phrases were proofread by SMEs multiple times to remove noises and to give feedback for algorithm optimization. Finally, the phrases were shortlisted to prioritize topics with high publication rates and good citation graph cohesiveness. The shortlisted emerging phrases which comprised a mix of biomaterials and applications were used to create focused search queries for the individual subtopics.

Following the abovementioned methods, we identified the ten most promising material types in this report. We then present their publication trends in journals and patents, highlight their diverse applications, and shed light on the rapid development of specific properties or substances. Our objective is to provide a comprehensive overview of the evolving landscape in this field and offer valuable insights for future directions. We trust that this report will serve as a valuable resource for researchers, agencies, and perhaps entrepreneurs and investors as well, empowering them in strategic planning and furthering their endeavors in this domain.

I. Hydrogels

Hydrogels are soft materials composed of three-dimensional polymeric networks that can absorb and retain high amount of water. They are hydrophilic and porous, exhibit crosslinked structure and infinite molecular weight, and do not dissolve in water. In the past two decades, hydrogels have drawn considerable attention from researchers due to their wide range of applications. **Figures 1A and 1B** demonstrate the increasing number of hydrogel-reporting journal and patent publications, respectively. The exponential growth in journal publications is evident over the past five years, while the number of published patents has shown relatively steady growth. Hydrogels can be of two types: Physical and chemical. The physical or reversible hydrogels are readily dissolved by altering the modulating factors like temperature, pH, and ionic strength of the solution.[6] In contrast, the network structure in the chemical hydrogels is formed by covalent bonding, therefore normally more stable and less reversible.

These materials possess tunable physical and chemical properties, making them highly versatile for various applications such as contact lenses, hygiene products, and tissue engineering. Moreover, some hydrogels can act as stimuli-responsive carriers for drugs or active biomolecules, providing both wound protection and facilitating wound healing.

Researchers have innovatively designed hydrogels tailored to specific applications. To achieve this goal, various feedstock materials, both natural and synthetic, have been explored. Based on origin, hydrogels can be natural, synthetic, hybrid, or semisynthetic.[7] Natural hydrogels, made of natural ingredients such as collagen, chitosan, alginate, hyaluronic acid, cellulose, and gelatin, are the most biocompatible and biodegradable with good adhesive properties.[8-10] However, natural hydrogels often have limitations in tunability and achieving certain unconventional properties. These limitations can be overcome by using synthetic hydrogels, which are more easily fabricated with tailored features than natural hydrogels. Therefore, synthetic hydrogels are mostly preferred in biomedical applications as long as their biocompatibility is ensured. Synthetic polymers such as Polyethylene glycol (PEG),[8-10] Polyvinyl alcohol (PVA),[11, 12] Poly acrylic acid (PAA),[13] and Polyethylene oxide (PEO)[14] are widely used to prepare synthetic hydrogels. Hybrid hydrogels are fabricated by the combination of natural and synthetic polymers to exploit the advantages of both.[15-17] Notably, synthetic hydrogels have become well-established materials in the field of applicative hydrogels, while natural hydrogels are still emerging.

To meet the requirements in various applications, numerous types of functional hydrogels have been fabricated in recent years. **Figure 1C** shows the emerging number of hydrogel-related journal publications based on their functionalities, including conductive, self-healing, tough, stimuli-responsive, injectable, shape memory as well as multifunctional hydrogels. For example, an ionic conductive hydrogel with hybrid latex particles demonstrates excellent mechanical adaptability mimicking the human skin, including good stretchability, robust electricity, rapid self-recoverability, and a low modulus.[18] The practical use of most hydrogels is restricted because of their limited toughness. To address this issue, a tough biocompatible hydrogel was developed with an adhesive side and high drug-loading capacity that enabled tendon gliding and strong adhesion to tendons.[19] Additionally, several reports were published based on the fabrication of hydrogels for use in food science,[20] tissue regeneration,[21] three-dimensional bioprinting,[22, 23] and other remarkable applications.

Figure 1D further classifies the hydrogel publications based on three prominent applications: Advanced drug delivery, tissue engineering, and antimicrobial activity/carrier functionality. Notably, natural hydrogels have dominated these application domains most likely because of their inherent biocompatibility. As previously mentioned, the number of published patents is considerably lower than that of the published journals. The feedstock-based distribution of the hydrogel in patents is shown using pie charts (**Figure 1E**). Interestingly, **Figure 1D** shows a variety of natural hydrogels have been explored in research published in journals. Particularly, chitosan and cellulose show faster growth rates both in drug delivery and antimicrobial. However, in patent publications, the types of hydrogels are very much dominated by

collagen and gelatin across different applications (**Figure 1E**). It is quite possible that there may be an increase of patent publications on chitosan or cellulose related hydrogels in drug delivery or antimicrobial areas in the near future.

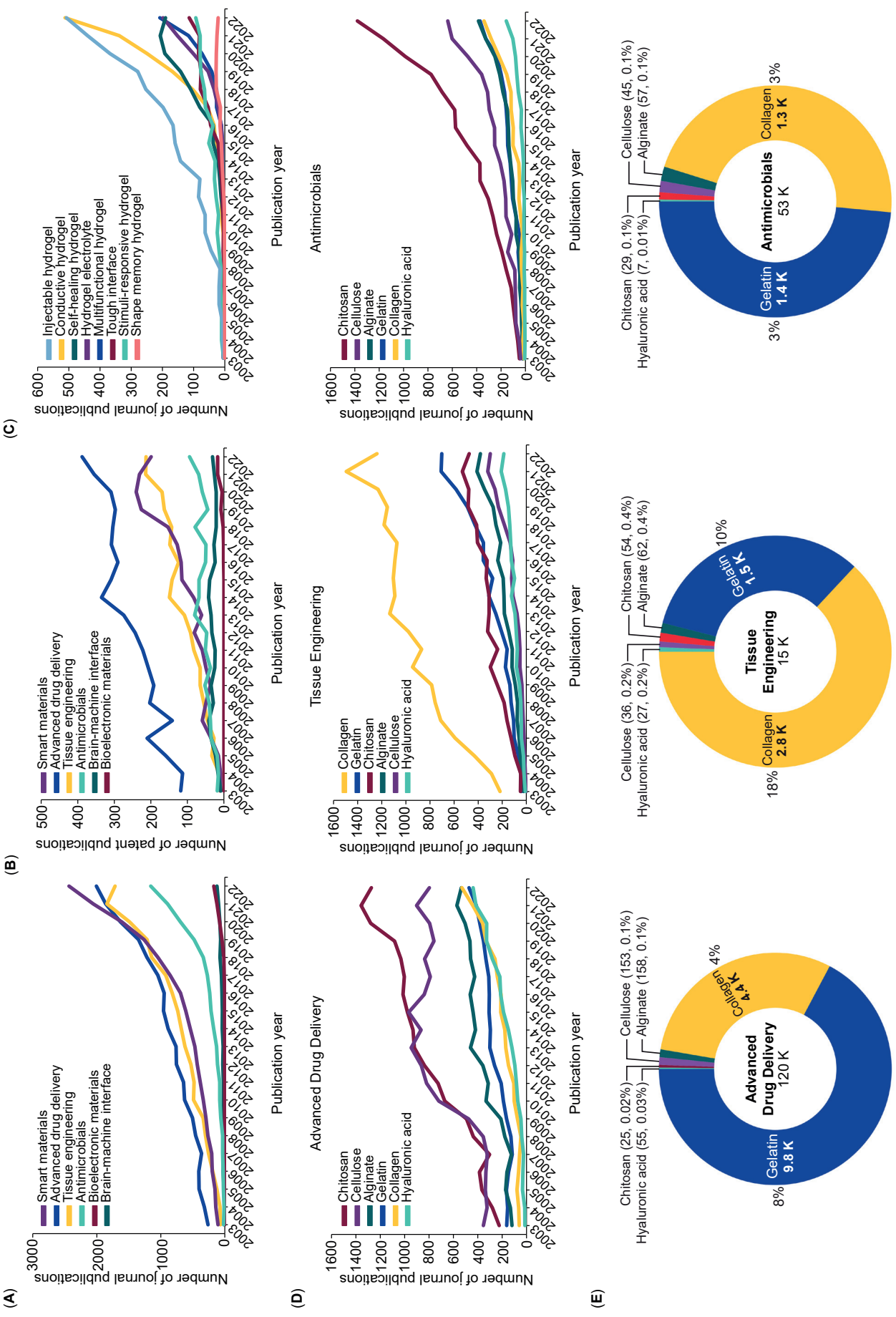


Figure 1. Growth of hydrogels across six applications – smart materials, advanced drug delivery, tissue engineering, antimicrobials, bioelectronic materials and brain-machine interface in terms of (**A**) journals and (**B**) patent publications over the last two decades (2003 to 2022). (**C**) Emergence of newer/novel types of hydrogels in terms of journal publications. (**D**) Shown across three major applications – advanced drug delivery, tissue engineering and antimicrobials – are the growths of six materials (chitosan, cellulose, alginate, gelatin, collagen and hyaluronic acid). (**E**) Distribution of aforementioned materials in patent publications over the same time period.

II. Antimicrobial materials

Antimicrobials are agents used to kill microorganisms and are classified as antibiotics, antifungals, antivirals, and antiparasitics, depending on the type of organism they target. Each category of antimicrobials presents its own set of challenges. In the last decade or so, the threat of antimicrobial resistance has become imminent and has been recognized by the World Health Organization (WHO) as "a global health and development threat" and "one of the top 10 global public health threats facing humanity".[24]

The primary challenge for antibiotics is the presence of superbug strains due to multi-drug resistance.[25] Resulting from a complex mixture of reasons (including socio-economic) and exacerbated by excessive use of antibiotics in humans and veterinary care, as well as in the meat industry,[26-28] this ever-growing risk has been compounded by a lack of discovery of novel antibiotics.[29-31] The COVID-19 pandemic has reiterated the importance of developing antivirals that can effectively target a broad range of viruses. One major challenge in the development of antiviral therapies is the emergence of resistance through viral mutations.[32, 33] The development of antifungals appears to have stagnated/proceeded at a slow rate due to challenges including high toxicity, lack of novel targets, and rapid development of resistance.[34-36] However, with the crises of climate change, the incidence of fungal infections affecting human beings is predicted to increase,[37] making the development of new antifungals an urgent need.

The analysis of CAS Content Collection shows that over the last two decades, there has been a constant growth in the number of journal publications focusing on the use of biomaterials in the field of antimicrobials. Interestingly, the growth in journal publications has been exponential over the last five years whereas the number of patents has grown at a relatively steady rate. Notably, the relative growth in journal publications suggests that antibacterial materials have the highest contribution, followed by antifungal, antiviral, and antiparasitic materials (**Figure 2B**). In terms of the type of material itself, nano-based systems have shown a tremendous increase in journal publications (**Figure 2C**). A closer look at CAS Content Collection shows that amongst nano-based systems, nanoparticles are the most prominent contributors to journal publications followed by nanofibers, nanocarriers, nanotubes, and nanosheets. Materials like nanorods, nanozymes, and nanowires contribute a smaller number of publications, but their overall trends appear to be emerging in the last few years (**Figure 2D**). Nanoparticles have been successfully employed as carriers of agents targeting bacteria,[38] fungi,[39] viruses,[40, 41] and parasites.[42] The nature and dimensions of nanomaterials appear to be critical for their antimicrobial activity with reports of metal (Ag, Au, Cu) and metal oxide (ZnO, CuO)[43] and polymer-based[44] nanoparticles being employed effectively. Other materials exhibiting growth in the past two decades are polymers, antimicrobial peptides, and hydrogels (**Figure 2C**). Antimicrobial peptides (AMP) are naturally occurring peptides that can be classified based on their antimicrobial target (antibacterial, antifungal, antiviral, or antiparasitic peptides).[45] A few FDA-approved AMPs include antibiotics such as gramicidin (CAS# 1405-97-6), vancomycin (CAS# 1404-90-6), and oritavancin (CAS# 171099-57-3).[46] Both, gelatin-based bioscaffolds and collagen-based nanocomposites/scaffolds featuring antimicrobial properties have been applied in wound healing[47-49] and tissue engineering (**Figure 2C, 2D**).[50]

In the field of emerging biomaterials, it is unsurprising that publications related to bacteria surpass those that are virus or fungi-related by ~15- and ~3-fold, respectively (**Figure 2E**). Within the category of bacteria, equal and major contributors are *Staphylococcus* and *Enterobacter*, Gram-positive and Gram-negative bacteria, respectively. This can be attributed to the presence of multidrug-resistant strains in both genera, *Staphylococcus* [51-53] and *Enterobacter*.[54] The other major contributors are comprised of gram-negative bacteria *Pseudomonas*, *Klebsiella, Salmonella*, and gram-positive bacteria *Bacillus* and *Streptococcus*. It is worth noting that most of the aforementioned bacterial genera also show an increasing incidence of antibiotic resistance.[55-60] The interest in developing biomaterial technologies in the antimicrobial field is geared toward overcoming resistance.[61] In the effort of developing antiviral drugs, the distribution of publications is skewed towards HIV and herpes, with influenza and coronavirus bringing in a close second (**Figure 2E**). Finally, in terms of fungi, the greatest interest appears to reside in the *Candida* genus (**Figure 2E**) which is a prevalent cause of fungal infections that is on the rise.[62] Other generas such as *Aspergillus*[63-65] and *Fusarium*,[66] also garner attention, especially in the context of infections among immune-compromised individuals.

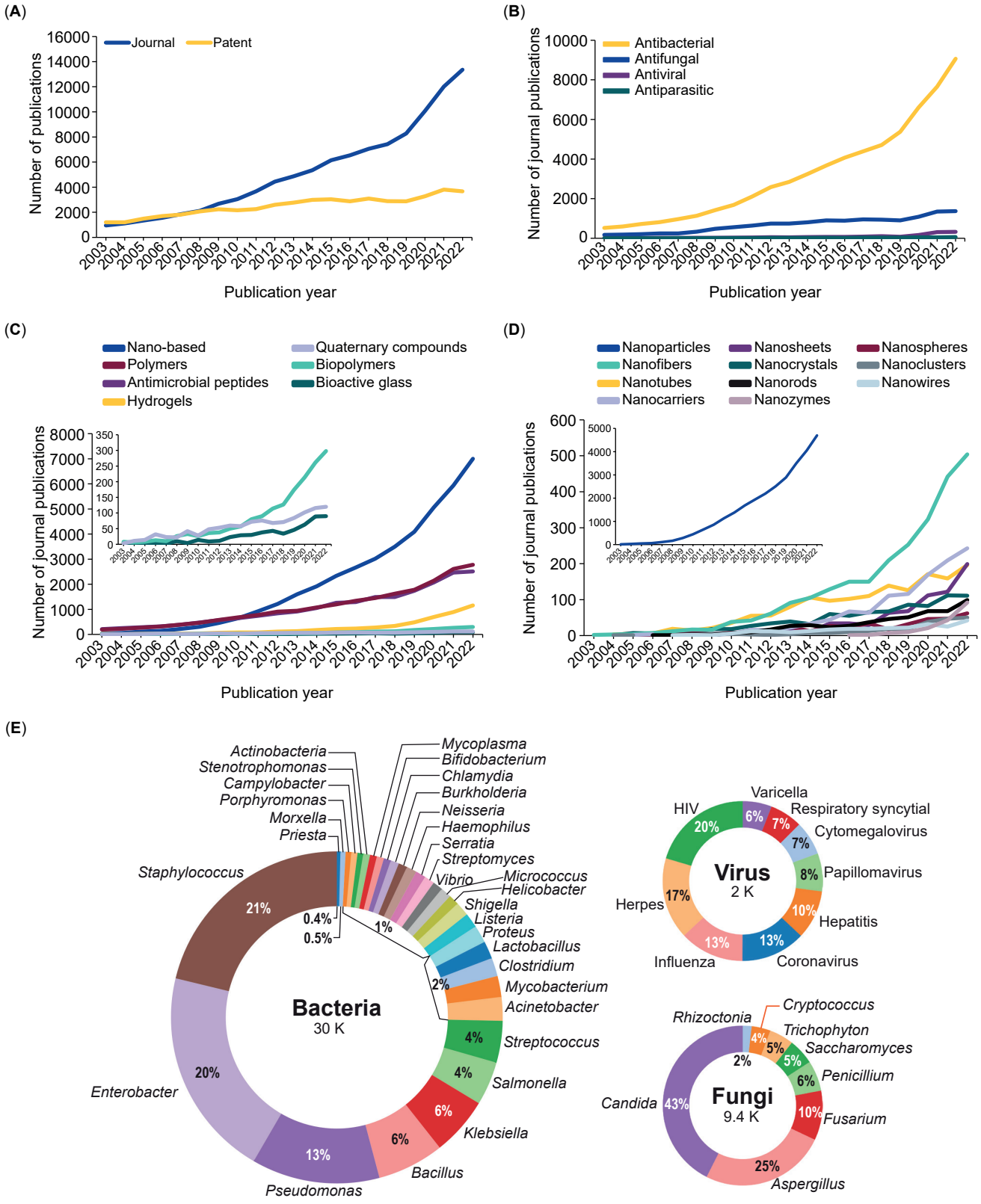


Figure 2. (**A**) Growth rate of publications in the field of antimicrobials across journals and patents over a period of two decades (2003 to 2022). (**B**) Relative growths in journal publications for the four main sub-categories: antibacterials, antifungals, antivirals and antiparasitic. (**C**) Emergence of materials in the field of antimicrobials – the tremendous growth of nano-based materials overshadows the relative growths of biopolymers, quaternary compounds, and bioactive glass (shown in inset graph for clarity). (**D**) Growth of nano-based systems in antimicrobials, data for nanoparticles is shown separately to allow clarity. (**E**) Distribution of publications (journals and patents) across the three main categories – bacteria, virus, and fungi. The number in the center of the donut chart corresponds to total number of publications for the respective categories.

III. Lipid nanoparticles

Lipid nanoparticles (LNPs) refer to nano-sized particles surrounded by a lipid bilayer membrane.[3] One of the major applications of the LNPs is as a drug delivery platform for efficient delivery of hydrophobic or hydrophilic drugs, including small molecules and various complex biologicals such as proteins and nucleic acids to the target cell. The recent successful use of lipid nanoparticles as a vital component in COVID-19 mRNA vaccines, where they played a key role in effectively protecting and transporting mRNA to cells, reinforces their applicability in drug delivery.[67-69]

Liposomes are the earliest types of LNPs and have been traditionally used for drug delivery[70, 71] (**Figure 3A**). Depending on the method of preparation, liposomes can either be surrounded by a single or multiple lipid bilayers giving rise to unilamellar vesicles or multilamellar/multivesicular vesicles respectively.[72, 73] The size of liposomes can vary from rather small (~25 nm) to large (~1 µm) vesicles. The vesicle size is an important parameter in regulating the circulation half-life of liposomes, and both size and the number of bilayers affect the amount of drug encapsulation.[74] In addition, their specialized structure helps them carry hydrophobic drugs within the hydrocarbon chains region of the lipid bilayer while the hydrophilic drugs can be encapsulated in the aqueous interior core. These features provide versatility to liposomes making them successful in delivering a wide variety of drugs including anticancer, antibiotic, anti-inflammatory, anesthetic, and other medicines. LNPs can also be used in wound healing, in diagnostic applications, as well as artificial cell models.[3, 67, 75] In fact, a significant part of the current knowledge regarding the structure and organization of biological membranes is based on studies on model lipid systems such as LNPs and particularly liposomes.[76]

Various types of LNPs exhibit structural and compositional variations. The simplest version of LNPs is the unilamellar liposomes, which have an aqueous core surrounded by a lipid bilayer (**Figure 3A**). Drug encapsulation in liposomes varies depending on their nature – thus, the hydrophilic and hydrophobic drugs are entrapped in the aqueous core and within the lipid bilayer, respectively. Despite their advantages and various applications, these unmodified LNPs lack selectivity, specificity and have low stability.[3] To overcome these disadvantages, modified LNPs such as targeted liposomes were developed. Targeted liposomes have ligands such as small molecules, peptides, and/or antibodies attached to their surfaces.[74, 77] These surface molecules could also be specific ligands, the corresponding receptors of which are over-expressed on cancer cells, inflammatory cells, etc., helping in selectively targeting such cells. Another type of modified LNPs, sterically stabilized ("stealth") liposomes have been also developed. They contain a polymeric coating, most commonly poly (ethylene glycol) (PEG).[78, 79] The inert and biocompatible PEG creates a steric barrier around the LNPs, allowing them to evade phagocytosis, thereby increasing their circulation half-life.[80, 81] Another specialized type of LNPs are the nucleic acid-carrying lipid nanoparticles. Specifically for the delivery of mRNAs, and they are designed to carry multiple (~100) mRNAs per LNP. These LNPs exhibit certain attractive features such as ionizable lipids which exhibit different charges depending on the surrounding pH, allowing them to both efficiently form stable complexes with negatively charged nucleic acids, and subsequently successfully release them.[81] More architecturally complicated, next-generation LNPs such as solid lipid nanoparticles, nanostructured lipid carriers, and nonlamellar LNPs like cubosomes, are well structured and thus show optimal stability. They also have high biocompatibility and loading capacity.[82] Cubosomes are made from lipid cubic phases consisting of single lipid bilayers that form a bicontinuous periodic lattice structure with pores formed by two interwoven water channels and stabilized by polymer-based outer coronas.[83, 84] Due to such diverse structural features, LNPs have various advantages such as high drug loading capacities, low immunogenicity, long-term stability, protection of drugs from degradation by external factors, enhanced drug bioavailability, improved drug release properties, and successful drug targeting. LNPs such as solid lipid nanoparticles also facilitate controlled and sustained release of the drugs at desired target locations.

To analyze the relative prevalence of each type of LNP's in publications, we conducted research using the CAS Content Collection. The result shows that immunoliposomes – a version of liposome functionalized with antibodies or their fragments, are the largest contributor accounting for ~50% of publications from 2003 onwards (**Figure 3B**).

Cationic liposomes which contain one or more type of cationic (positively charged) lipid results in the formation of the positively charged lipid bilayer that can form complexes with negatively charged nucleic acids. Cationic liposomes are another major publication contributor followed by PEGylated ("stealth") liposomes. LNPs such as solid lipid nanoparticles, nanostructured lipid carriers, and cubosomes, have contributed a lesser number of publications, indicating the recent interest of researchers in these structures when compared to more traditional ones. When we visualize publication trends for each type of liposome over the last two decades, we observe that immunoliposomes still show an emerging trend (**Figure 3C**). Interestingly, solid lipid nanoparticles and cubosomes both demonstrated fast growth rates. Indeed, solid lipid nanoparticles have steadily became the preferred LNP type for various applications due to their stability, higher drug loading capacity, improved drug release properties, long-term colloidal stability, and better oral bioavailability of hydrophobic drugs.[82, 85-87]

While LNPs have emerged as promising drug delivery platforms, they do have certain limitations, such as the use of high quantities of synthetic lipids, especially in the cationic LNPs, can lead to toxicity. Therefore, these should be replaced by LNPs with lesser quantities and safer lipids. Another important concern regarding the safety of LNPs results from PEG conjugates leading to certain immune reactions such as accelerated blood clearance (ABC). This involves the production of anti-PEG antibodies at initial injection, which causes accelerated clearance upon subsequent injections. PEG conjugated LNPs can also produce a hypersensitivity reaction referred to as complement activation-related pseudoallergy (CARPA). These adverse immune reactions are important determinants that enforce the need of safer LNP based drug formulations.[79]

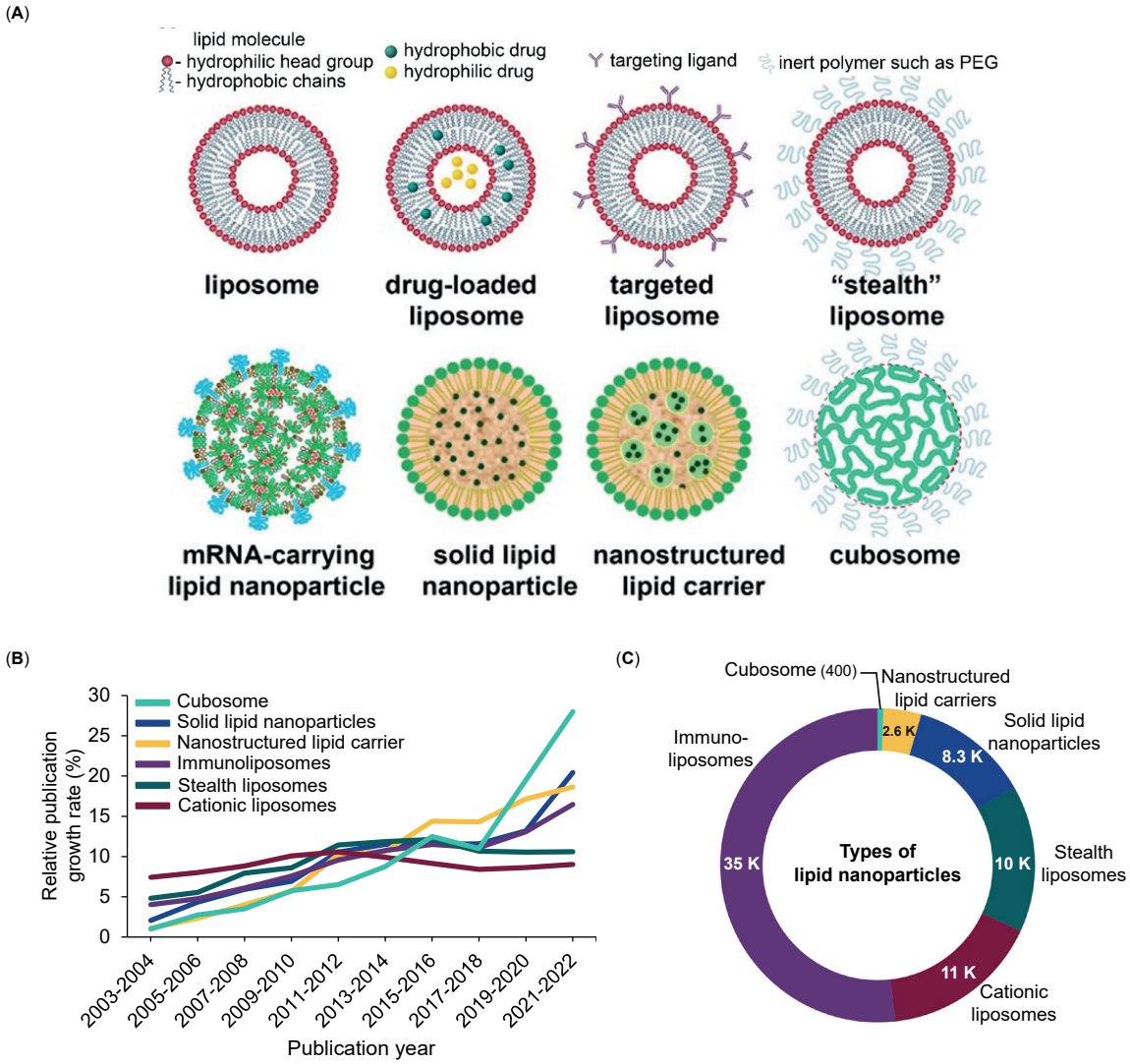


Figure 3. (**A**) Schematic representation of the different types of lipid nanoparticles. Adopted from Tenchov et al.[3] (**B**) Distribution of publications (journals and patents) across different types of lipid nanoparticles indicating rapidly growing interest. (**C**) Growth of different types of lipid nanoparticles over the past two decades.

IV. Exosomes

Exosomes are nanosized (diameter ~30–150 nm) extracellular vesicles enclosed by a lipid bilayer.[88-90] They are secreted by most eukaryotic cells and capable to facilitate intercellular communication by transferring bioactive cargo including proteins, nucleic acids, and lipids to target cells.[91-93] In addition to their role in cell-to-cell communication and signal transduction, exosomes are also crucial for supporting and remodeling the extracellular matrix, generating immune response, tissue homeostasis and regeneration. They are also involved in development of diseases such as cancer, neurodegenerative, and cardiovascular disorders.[91, 94-96] Exosomes' distinctive properties – innate stability, low immunogenicity, biocompatibility, and good biomembrane penetration capacity – allow them to function as superior natural nanocarriers for efficient drug delivery. Their capability in crossing the blood brain barrier makes them ideal delivery vehicle to brain. Furthermore, exosomes are also favorable in clinical diagnostics, as they hold various biomolecules from host cells, which are indicative of pathophysiological conditions.[97-100] However, exosome biogenesis is a complex process and various pathways have been identified for it. One of the most predominant ways for exosome biogenesis is through the endocytic pathway as shown in **Figure 4A**.[97, 101, 102]

A closer examination of the biological composition of exosomes reveals that based on the nature of the donor cell, they contain various membrane-bound proteins such as tetraspanins, heat shock proteins, membrane transport proteins and fusion proteins.[99, 103, 104] Certain surface proteins can be artificially expressed to target exosomes to the right cell/tissue. The exosome membrane bilayer also contains lipids such as cholesterol, sphingomyelin, ceramides, saturated phosphatidylcholines, and phosphatidylethanolamines, at concentrations higher than that of the plasma membrane. The lumen of exosomes contains nucleic acids such as DNA, mRNA, microRNA (miRNA), and non-coding RNA (ncRNA) in addition to cargo peptides, proteins, and metabolites. Some of these components can also act as diagnostic markers.[92, 93] (**Figure 4A**).

Due to aforementioned properties and advantages, exosomes are a topic of continued scientific interest, as revealed by the search conducted in the CAS Content Collection. Journal publications pertaining to exosomes have shown an exponential growth over the years from 2011 onwards (**Figure 4B**). Notably, during the initial years (2003-2011), the number of patents appears to be significant; however, their overall growth appears to have increased relatively slowly when compared to the growth in journal publications, over the years. Exosomes have been preferred as drug delivery vehicles due to their abundance, biocompatibility, low immune response generation, presence of specific markers, and ability to mediate cellular communication.[95, 98, 99] Another particularly promising clinical application of exosomes is in diagnostics. They incorporate various biomolecules from host cells, which are indicatory of pathophysiological conditions, therefore they are considered vital for biomarker discovery in clinical diagnostics. Recently, exosomes derived from adipose tissue stem cells have also been reported to promote wound healing.[90, 98, 105]

Therapeutic agents and bioactive cargo can be introduced into exosomes either before or after their isolation. Multiple methods are used for loading the exosomes; out of these methods, electroporation appears to be the most preferred one followed by transfection and freeze-thaw (**Figure 4C**).[89, 106, 107] Other methods such as extrusion and incubation are also used for exosome loading, however, they are used less frequently. An important prerequisite for all exosome-related applications is the isolation and purification of exosomes at a large scale.[108-110] Various methods such as ultracentrifugation, size exclusion chromatography, ultrafiltration, polymer-induced exosome precipitation, microfluidics, immunoaffinity based techniques, asymmetric flow field-flow fractionation and aptamer-based methods are used for purifying exosomes from sources such as tissues, body fluids including serum, blood, urine, CSF, and milk samples, etc.[111-117] The major challenges encountered are difficulties in scaling up of production, lack of standardized purification and analysis methods which results in low yield, and batch-to-batch variations.[110, 118] Thus, developing efficient and reliable isolation and characterization techniques is critical to further advance in this area.[109, 118, 119] Although there are no approved exosome drugs at the market yet, this holds so much promise that there are already hundreds of ongoing clinical trials exploring the use of exosomes[76] for treating a variety of diseases, including cancer, neurodegenerative disease, stroke, depression and so on.

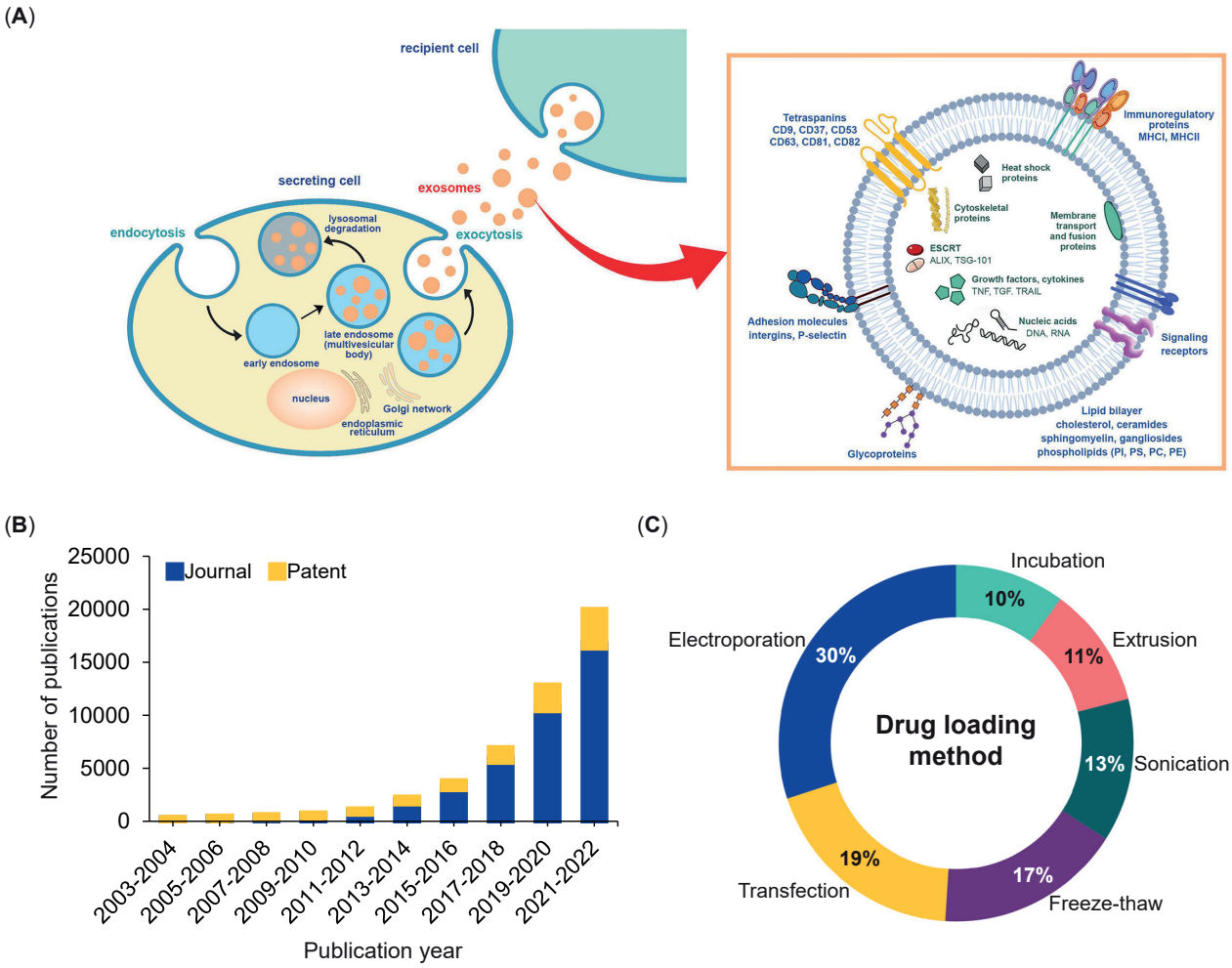


Figure 4. (**A**) Schematic representation depicting biogenesis and secretion of exosomes, adapted from Tenchov et al[104]. (**B**) Overall growth of publications pertaining to exosomes over 2003-2022 across journals and patents. (**C**) Percentages of documents related to exosome applications in therapy and diagnostics concerning various exosome loading methods.

V. Bioinks

Bioinks refer to any natural or synthetic material used in three-dimensional bioprinting (3DBP) primarily in the form of cell-laden hydrogels. The fabrication of bioink materials has allowed the creation of complex biological constructs with desired biological and biochemical environments.[120] 3DBP enables the fabrication of biomimetic scaffolds that exhibit desirable features and controlled spatial organization of cells and other biomaterials to mimic natural tissue/organs. An ideal bioink material should possess crucial features such as high mechanical robustness, bioprintability, insoluble in the cell culture medium, biodegradable at a rate that matches with the tissue regeneration, low-immunogenicity, and low-cytotoxicity. In addition, it should promote cell adhesion. As a result, numerous biomaterials have been prepared with intended usage in regenerative medicine and tissue engineering.[121, 122]

Over the past few decades, there has been a stagnation in the number of successful drug development projects.[123] In addition to other factors, the inadequate reliability of preclinical models significantly contributes to the overall low success rate. The live structures created by 3DBP afford several remarkable advantages, such as accelerating the drug development process and increasing the success rate of drug candidates in clinical trials. For instance, three-dimensional scaffolds made of bioinks can provide cells with three-dimensional culture environments in which several physiologically and functionally relevant human cell phenotypes can be continuously maintained.[124] To improve the predictions regarding the clinical efficacy and safety of a new drug candidate, researchers are currently interested in the 3D bioprinted culture environments. In organotypic and microphysiological cell culture, human cells can be cultured for weeks to months, enabling long-term investigations such as pharmaceutical ADME studies.

Furthermore, a major global public health concern is to the shortages of tissue/organ supplies. According to the World Health Organization, only 10% of the worldwide requirement can be currently satisfied. 3DBP using bioinks can create bioartificial organs with minimum immune rejections. However, several intermediate goals need to be successfully achieved to make the concept of 3D bioprinted organs a success.

The 3D environment created by the hydrogel closely mimics the natural extracellular matrix and provides cells with proper nutrition and oxygen flow, increasing the cell survival in the bioprinted constructs by up to 90%. Furthermore, several 3D tissue/organ models have been fabricated using hydrogels, which have made significant contributions to drug testing, preclinical treatment efficacy, and enable the replication of complex organ anatomy.[22, 125] As shown in **Figure 5A**, the increasing number of journal and patent publications that related to bioink over the past two decades clearly reflects the applicability of these materials for tissue/organ regeneration studies. Notably, the most reported bioink materials comprise collagen, stem cells, transcription factors, fibroblasts, and extracellular matrix (**Figure 5B**).

A composite hydrogel prepared by blending collagen with silk has functioned as an ideal skin mimic.[126] 3DBP has also been employed to create multilayer structures that mimic the brain to promote neuronal growth and establish brain networks.[127] These bioprinted brain-like structures have made significant contribution to the understanding of brain functions, brain injuries, and neurodegenerative diseases. Multichannel biomimetic scaffolds produced by 3DBP have been utilized to provide long-term personalized clinical implants for patients with spinal cord injuries.[128] Several research groups have exploited 3DBP for tissue/organ regeneration, such as printing cardiac tissue or partial organ,[129, 130] bone tissue engineering,[130, 131] cartilage regeneration,[132] and printing multilayered liver-like structures.[133] The pie chart in **Figure 5C** illustrates that bone and regeneration dominate the applications of 3DBP using bioinks in terms of published reports. Among the organs that have been 3D printed, the liver occupies ~80% of the publication space.

However, the clinical translation of 3DBP is still awaiting. To date, the progress with 3DBP has been limited to preclinical research. 3DBP of human solid transplanted organs has not yet been realized. Clinical trials are available that analyze the safety and effectiveness of dentures, bone defects implants, and orthopedic devices.[134, 135] The introduction of the BioPen, an in situ 3DBP technology, is one of the newest applications on the horizon.[136, 137]

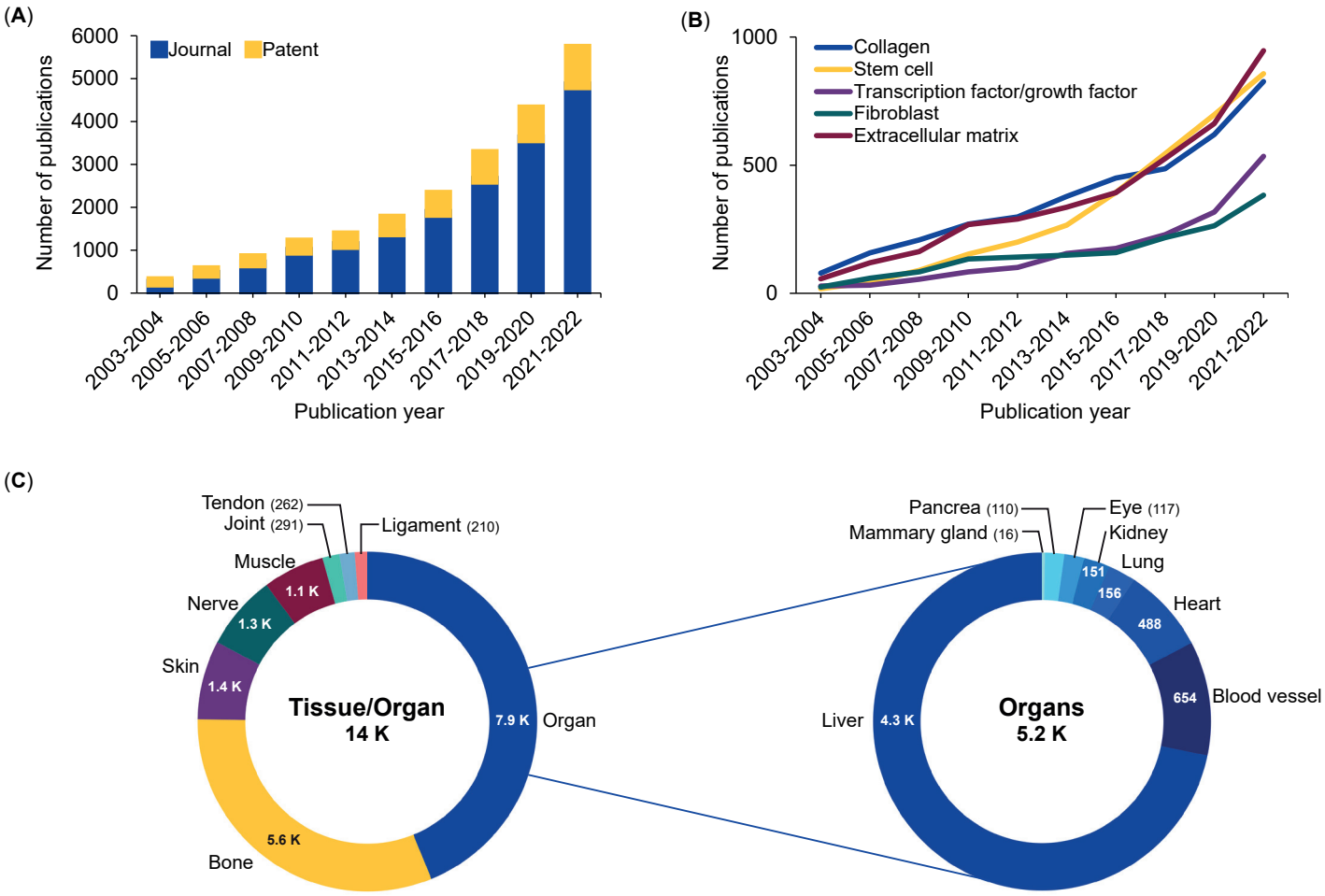
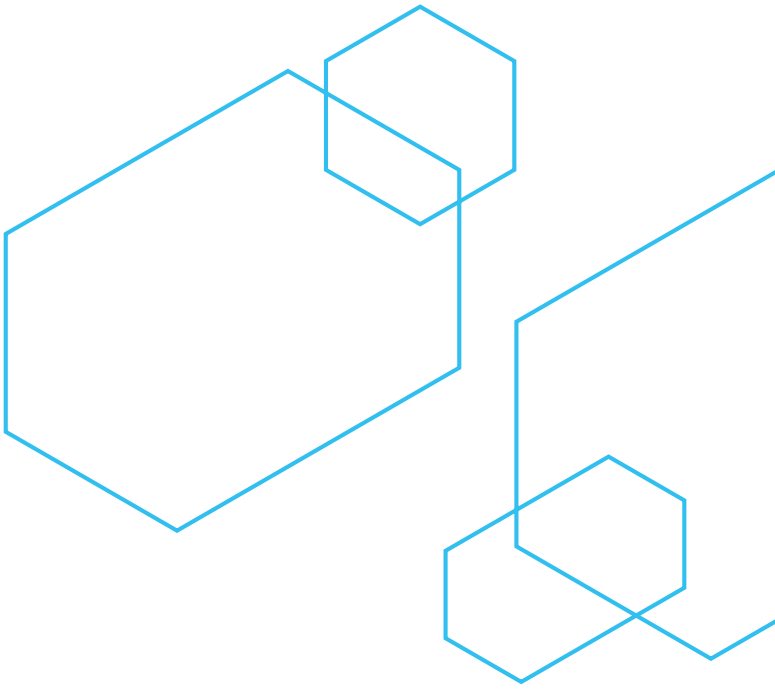


Figure 5. (**A**) Growth of publications in the field of bioinks as mined from the CAS Content Collection over the period of 2003-2022. (**B**) Emergence of materials such as collagen, stem cell, transcription factor, fibroblast, and extracellular matrix in the field of bioinks. (**C**) Donut charts representing distribution of publications across different tissue and organ systems with the right chart showing in greater detail applications of bioinks across different types of organs.

VI. Programmable biomaterials

Programmable biomaterials are dynamic biomaterials that can change their properties and shapes based on user signal input in response to stimuli or by sensing a change in their immediate environment.[138, 139] The interest in programmable biomaterials, which are considered next-generation biomaterials, has been gaining momentum in the last decade as reflected by the increase in publications, especially in journals (**Figure 6A**). The ability of programmable biomaterials to respond to external stimuli enables the designing of intelligent devices or "live" devices. These materials can adopt a conformation/structure/shape that is distinct from their original shape with a capability of returning to their original state.[139] The most extensively used materials are shape memory polymers (SMPs) (**Figure 6B**), which can be classified as one-way[140] or two-way SMPs[140, 141] depending on their ability to transform between various shapes. One-way SMPs can recover their original shape from a deformed temporary shape when exposed to a specific stimulus. In contrast, two-way SMPs have the ability to transition between two or more distinct shapes in response to different stimuli, offering greater versatility in shape-changing capabilities.[140]

An intriguing application that has been gathering interest in the last decade is 4D printing, which is basically 3D printing with the added element of time.[142, 143] However, according to the more nuanced definition, a 4D-printed structure is one that is capable of undergoing changes in property or shape when subjected to stimuli[143] over time. Polymers, often used in 4D printing, show a steady growth in terms of the number of publications in the past two decades (**Figure 6B and 6C**) and this is indicative of the burgeoning interest in 4D printing. In addition, publications related to hybrid materials primarily composed of polymers and supplemented with nanoparticles[144] have also steadily grown during the period (**Figure 6B and 6C**). Other emerging materials commonly used in this field include metal-based materials,[145, 146] hydrogels,[147] and silk-based materials[148, 149]. The interest in materials capable of biomimicry (including DNA-based and peptide-based) is also rising[150] in this field (**Figure 6B and 6C**). Metal-organic frameworks show a sudden sharp rise in publications since 2018 (**Figure 6C**) and can be attributed to MOF-based composite films demonstrating applications in robotics[151] and catalysis.[152] The types of stimuli that programmable materials respond to are diverse, but the most common ones are pH,[153] magnetic field,[154, 155] light,[156] and temperature[157-160] (**Figure 6D**). While not as prolific as the aforementioned stimuli, mechanical stimuli,[147] osmotic pressure,[161] and electrical field[162] are also deployed in programmable materials (**Figure 6D**). Materials capable of responding to more than one stimulus also exist[163] and exhibit remarkable potential for applications. It is undoubted that programmable materials offer the potential to make remarkable advancements in the field of biomedical sciences.



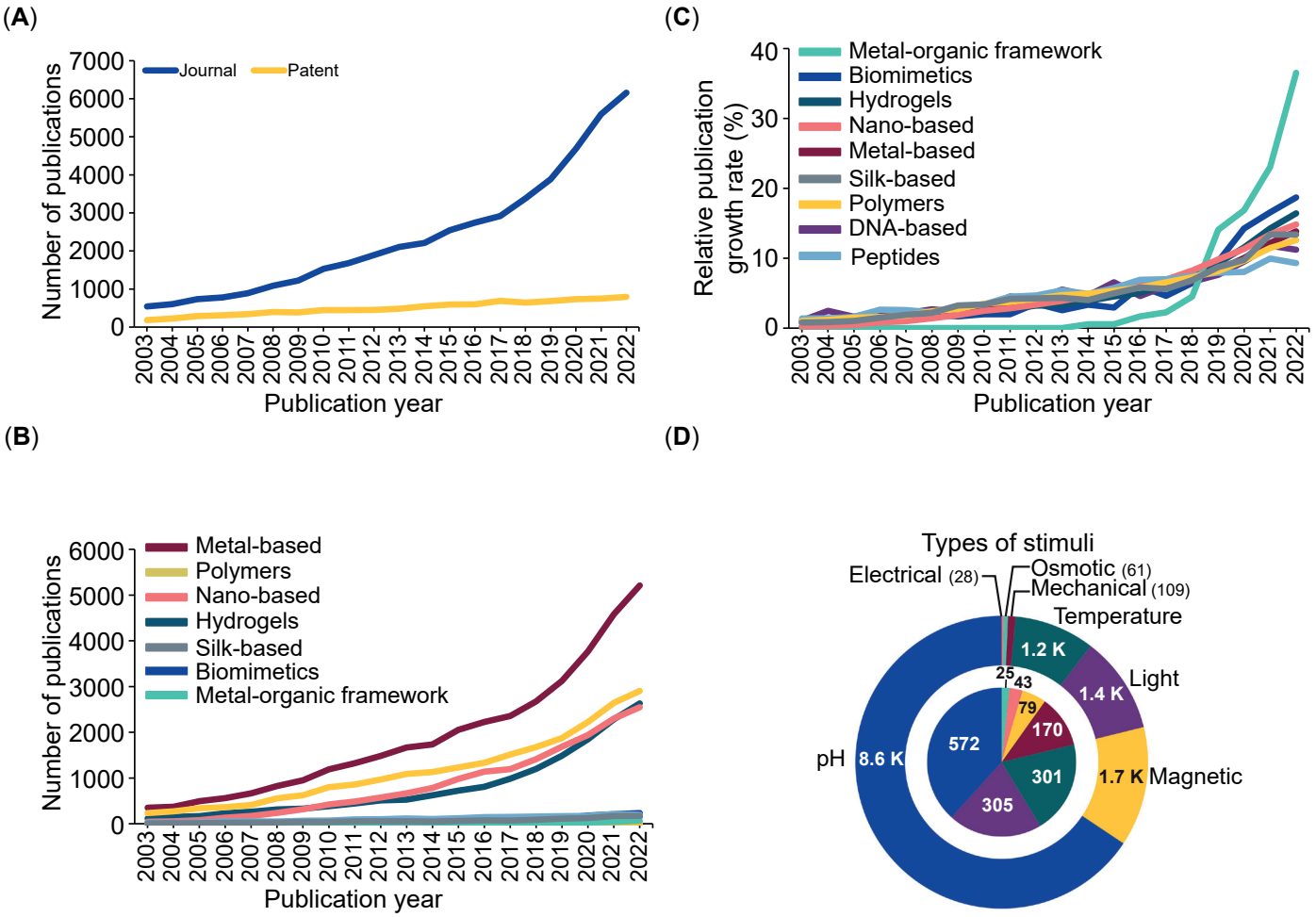


Figure 6. (**A**) Publication trends in programmable materials over a period of nearly two decades in terms of publications – journals and patents (shown as solid blue and yellow lines, respectively). Growth rates of emerging biomaterials in terms of (**B**) absolute number of publications and (**C**) relative publication rate in the field of programmable materials over 2003-2022. (**D**) Distribution of biomaterials responsive to different types of stimuli (pH, temperature, light, mechanical, electrical, magnetic, osmotic) in programmable materials. The outer donut and inner pie charts correspond to journal and patent publication data from 2003 to 2022, respectively.

VII. Protein-based materials

Proteins are natural polymers made up of amino acids. Protein-based biomaterials such as silk, collagen, fibrin, keratin, elastin, and resilin are biocompatible, bioabsorbable, and biodegradable.[164, 165] As is evident from **Figure 7A**, journal publications in this field show a consistent increase in the last two decades. Though less in number compared to journal publications, patent publications also demonstrate a steady increase over the years. These rising trends in combination with high publication numbers indicate a growing interest among researchers in this field.

To further analyze various types of proteins used in developing advanced protein-based materials, we used CAS Content Collection to reveal that gelatin, peptides, collagen, extracellular matrix (ECM) proteins, antibodies, albumin, keratin, silk, elastin, resilin, and talin are prevalently used (**Figure 7B**). Notably, gelatin and collagen contribute more than 40% of the publications in this field. Resilin, talin, and elastin have a relatively small overall contribution in terms of publication numbers, but they show an increasing publication rate over the last few years indicating their emerging trends (**Figure 7C**).

Gelatin, a protein substance derived from collagen, is biocompatible, absorbable, and biodegradable, and therefore it finds use in applications such as tissue engineering, wound healing, and injectable fillers.[166] During the past decade, photo-crosslinked hydrogels made using gelatin methacryloyl (GelMA), a gelatin derivative, have gained attention for its use in developing 3D-printed scaffolds, injectable hydrogels, and micropatterns for tissue engineering and regenerative medicine. Additionally, they are also used in packaging.[167-171] Collagen itself, a fibrous protein present in the extracellular matrix of animal tissues, is another useful biopolymer. Cross-linked collagen-based materials, collagen scaffolds, films, and hydrogels are employed in tissue engineering, wound healing, and tissue repair and regeneration.[165, 172, 173]

Silk is one of the best-known proteins used for developing advanced protein-based biomaterials.[174] It is a fibrous protein that has been used in medicine since ancient times to develop surgical sutures.[175-177] Regenerated silk fibroin (SF) can be fabricated into various forms such as hydrogels, films, fibers, nanoparticles, cryogels, and sponges and used in various applications.[176, 178, 179] Silk sericin (SS), another silk glycoprotein that helps in joining silk fibroins, acts as a 'glue' and is therefore useful in tissue engineering and cell culture.[177, 180] Our analysis of data from CAS Content Collection reveals that silk-based materials are mostly used in tissue scaffolding and tissue engineering, designing coating materials, implants, wound dressing, drug delivery, and developing biosensors (**Figure 7D**). In addition, proteins like keratin can be cast into films, composites, sponges, and hydrogels to be used in various applications ranging from biomedicine to water purification.[181, 182] Albumin, a well-known plasma protein is used as a coating material to enhance cell adhesion; therefore it finds extensive uses in tissue engineering and wound healing.[183] It is also used to develop pH and redox-sensitive hydrogels for targeted drug delivery.[184, 185] Other proteins such as elastin and its derivatives such as elastin-like peptides (ELPs) and elastin-like recombinamers (ELRs) are used in preparing materials such as skin and vascular grafts and elastic cartilage, and in wound healing and drug delivery.[186, 187] Proteins such as ferritin, some heat shock proteins (HSPs), and eukaryotic vault proteins can also be used to design protein nanocages that are formed by the self-assembly of multiple subunits forming hollow cage-like structures of nanometer size. These protein nanocages (PNCs) are popular for designing targeted drug/vaccine delivery.[188-190] Finally, with the advent of newer recombinant DNA-based technologies and advancements in computational design and synthetic biology, newer and advanced protein-based materials can be developed, thus expanding their applicability to other areas.

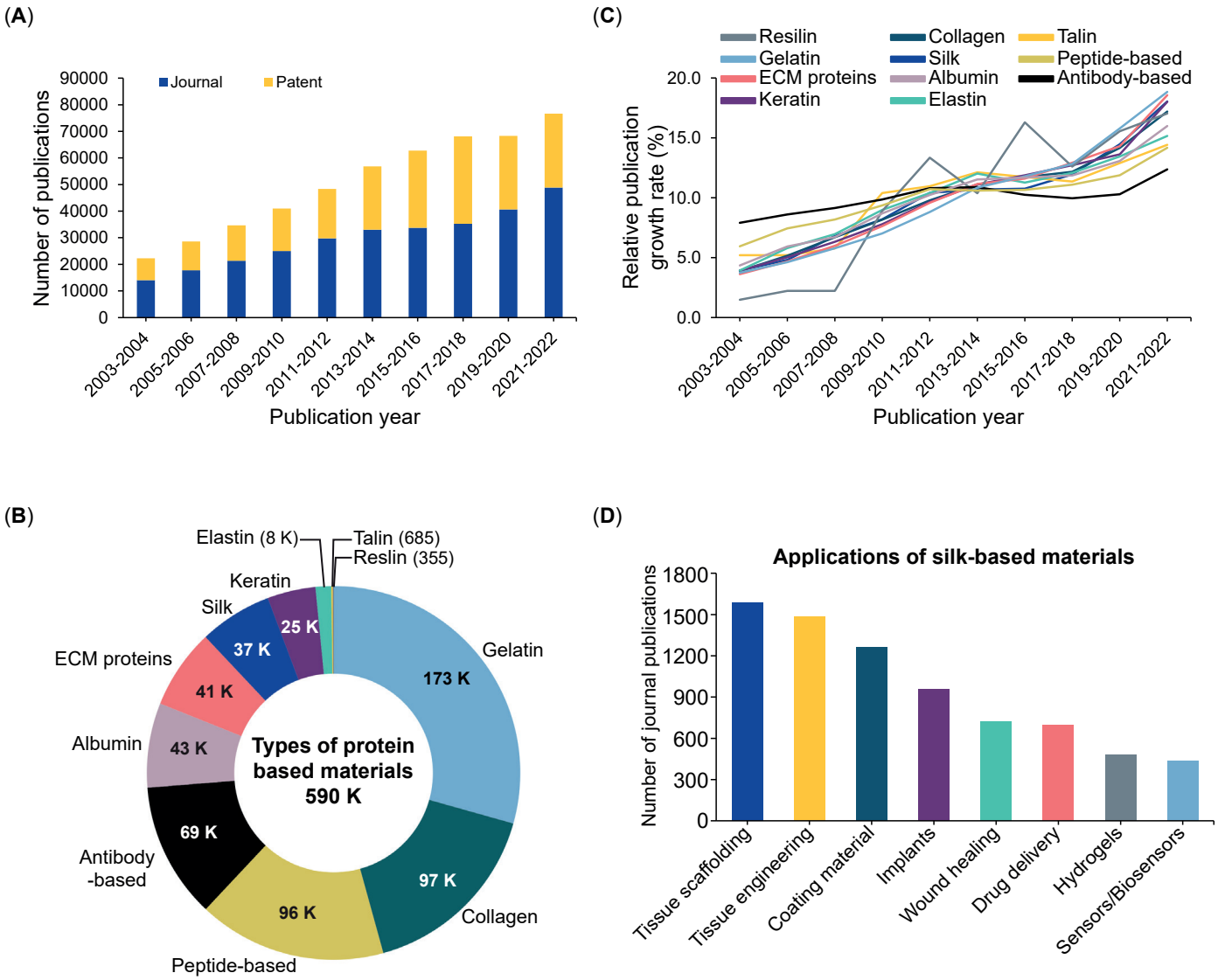


Figure 7. (**A**) The growth rate of publications in the field of advanced protein-based materials across journals and patents over a period of two decades (2003 to 2022). (**B**) Distribution of various proteins used for developing advanced protein-based materials. (**C**) Distribution of journal publications across various categories of advanced protein-based materials indicating their emerging growth trend. (**D**) Distribution of major applications of silk protein-based materials.

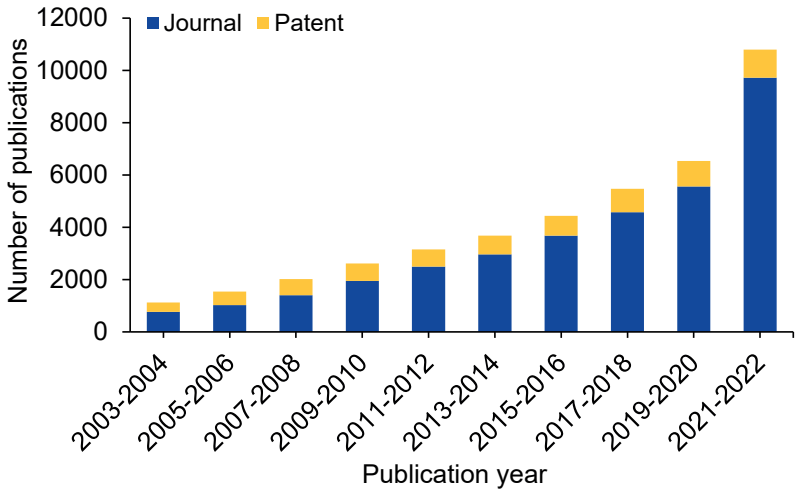
VIII. Self-healing biomaterials

Materials that possess the capacity to heal minor damages resulting from prolonged mechanical wear (usually sustained as a part of normal/regular use) are termed self-healing materials.[191] This unique ability of self-repair is attractive because it increases the longevity of the material, negates requirement for maintenance and replacement, and reduces waste. In the biomedical field, this translates to sustained functional performance of medical implants, scaffolds, devices, and biosensors. The field of self-healing biomaterials has grown steadily in the last two decades (**Figure 8A**) and is primarily dominated by materials such as hydrogels,[21, 192, 193], hydrogel composites,[194, 195] and polymers[196] including biopolymers[197, 198] (**Figure 8B**). Self-healing materials often possess properties such as responsiveness to stimuli, mechanical tunability, shape-memory behavior and flexibility/malleability,[199] and exhibit a degree of overlap with programmable materials. Self-healing materials can be broadly classified into one of two categories, autonomous and non-autonomous, depending on the absence or presence of a trigger behind the self-healing behavior. Often the external stimuli can be a change in pH[200] or temperature.[201] Materials capable of self-healing at human body temperature[202] are particularly attractive in biomedical sciences. The ability to self-heal is often measured with respect to two major yardsticks – degree of wound closure and functionality recovery.[203]

Perhaps one of the most widely explored materials in the field are polymers for example dynamers or dynamic covalent polymers which are characterized by the presence of reversible covalent bonds between monomeric units, which allows/accommodates (confers) for self-healing behavior.[199] Key biomedical applications of dynamers include wound healing,[204] drug delivery,[205] and bio-imaging.[206] Self-healing hydrogels that take advantage of coordination bonds (instead of covalent bonds as conventionally designed) have recently gained traction.[207] The biomedical applications of self-healing hydrogels include drug delivery[208] and tissue engineering.[21, 192] MXene-hydrogel composites, capable of electroconductivity attributable to the MXene component, are being actively explored in the treatment of spinal cord injuries.[209] Other chemical interactions that are important for self-healing materials include noncovalent interactions such as hydrogen bonds,[210] ionic interactions,[211] van der Waals forces,[212] guest-host interactions,205 and biorecognition motifs.[196, 213, 214] The development of photoresponsive DNA-based self-healing materials have opened doors to potential biomedical applications.[215] These, along with other biomacromolecular materials such as polypeptides,[216] a type of biopolymer, dare being increasingly explored. They possess additional advantages of increased biocompatibility as well as low inherent toxicity compared to synthetic self-healing materials.

Self-healing biomaterials by virtue of their properties often serve as ideal candidates for development of electronic-skin (E-skin).[217, 218] E-skin or ionic skin (I-skin) are defined as types of smart skin composed of artificial materials capable of mimicking properties of natural skin.[219, 220] They have a wide range of biomedical applications including wearable devices that could be used for health monitoring[221] and prosthetics.[222] Incorporation of sensors capable of sensing stimuli such as temperature and mechanical[223] bring us one step closer to developing e-skins whose sensitivities are similar to natural skin. Recently, researchers have incorporated antibacterial properties into E-skin rendering it capable of killing E Coli and S aureus.[224] Such incorporation of antibacterial properties into self-healing material holds a lot of promise/potential for biomedical applications especially in wound healing and tissue engineering.[225-227] Thus, continued and growing exploration of novel self-healing materials have exciting implications in biomedical applications.

(**A**)



(**B**)

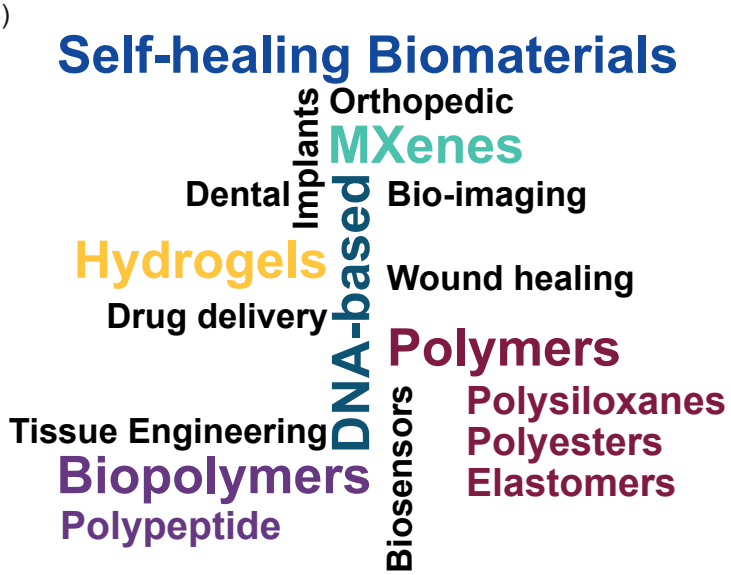


Figure 8. (**A**) Steady growth in publications related to self-healing materials over the past two decades (2003 to 2022) (**B**) Graphical representation of popular self-healing materials and their applications.

IX. Bioelectronic materials

Bioelectronics refers to devices and implants that can be integrated into the biological systems such as the human body. The constant need for healthcare, especially among the elderly and diseased population, necessitates the development of such systems.[228] Bioinformation digitalization and monitoring are more efficient ways than traditional methods, while also facilitating real-time monitoring and data analysis. These devices range from wearable devices such as smart watches, sensors,[229] monitoring devices used in healthcare settings to implantable monitoring devices. For materials to be part of these devices, especially those which are implanted, unique characteristics, such as biocompatibility and softness, are needed.

As is evident from the bioelectronics-related publications, this area has been growing at a steady phase in the last two decades (**Figure 9A**). However, the low patent/journal ratio indicates that most of the studies have not reached a point of commercialization. **Figure 9B** shows the bioelectronic applications demonstrating growing trends in recent years and high numbers of publications. Electrodes and biosensors that are closely related to each other seem to be the major applications in bioelectronics followed by neural network modeling and signal transduction. Publications related to electronic skin only began in 2015 but have since grown rapidly.

Figure 9C shows the materials selected based on their high growth and the number of publications. The major categories of materials used in bioelectronics are hydrogels, carbon-based materials, nanomaterials, semiconductors, and polymer films. No dominant class of materials can be observed in this area. Hydrogels show the highest growth in recent years, owing to their unique properties. Polymers, particularly conducting polymers, are another class of materials widely used as substrates and fillers in bioelectronics to render the devices stretchable and flexible. Semiconductors have been traditionally used in electronics and recently are getting replaced by nanosized semiconductors and organic polymers owing to their flexible nature. Overall, across most of the categories of materials, China has published the highest number of publications, followed by the United States, Republic of Korea, Japan and Germany (**Figure 9C**). Interestingly, the number of patents in hydrogels and polymers are either similar to or higher than the number of journal publications, highlighting the extensive commercial interest in these two types of materials.

Hydrogels have become an attractive option in bioelectronics as they occupy the middle ground between the wet and soft living tissues and the dry and hard synthetic materials.[230] Hydrogels made of poly(ethylene glycol)[231] and poly(vinyl alcohol) are used as coatings on devices made of materials such glass, silica and polydimethylsiloxane (PDMS). Another advantage of hydrogels is that they can be made conductive by adding salts such as NaCl and LiCl to polymer-based hydrogel, which are used as electrodes in biomedical applications.[232] In addition to ionically conductive hydrogels, electronically conductive hydrogels for are prepared by making composites with nanomaterials such as metal, carbon nanotubes, graphene, and metal nanowires. Gold nanowire-embedded hydrogels find applications in bioelectronic cardiac patch.[233] Conducting polymer hydrogels made of poly(3,4-ethylene-dioxythiophene) (PEDOT), poly(pyrrole), and poly(aniline) are intrinsically conductive and widely applied in neural implants, implantable sensors, prosthetic interfaces, and controlled drug delivery.[234]

In addition to the traditional polymers such as polyethylene, PDMS, polylactic acid (PLA), polyethylene glycol (PEG), and polylactic-co-glycolic acid (PLGA), natural polymers such as silk, shellac, gelatin and cellulose are used as substrates for bioelectronic devices.[235] Conducting polymers such as PEDOT:polystyrenesulfonate (PSS) mixture,[236 237] poly(3-hexylthiophene) (P3HT),[238] polypyrrole,[239-241] and polyaniline[242] are used as conducting fillers to add flexibility and sometimes as replacements for traditional inorganic conductors.

Nanomaterials are another class of materials that are used in bioelectronics owing to their unique electrical, electronic, mechanical, optical, chemical, and magnetic properties. Some of the most prevalent nanomaterials are carbon nanotubes, graphene, nanosheets, and nanowires.[243] Biosensors based on silicon nanowires containing field effect transistors (FETs) have demonstrated notable efficiency.[244] Owing to their excellent

mechanical strength, chemical and thermal stability, carbon nanotubes have been used in bioelectronic applications such as in vivo and in vitro detection, imaging and drug delivery.[245] Carbon nanotube-based FETs have a high potential in biosensing applications.[246] Another carbon-based nanomaterial, graphene, with favorable electronic and mechanical properties is also widely used in biosensor applications. Nanomaterials have an advantage over others in the injectable bioelectronic devices owing to their size.[247, 248]

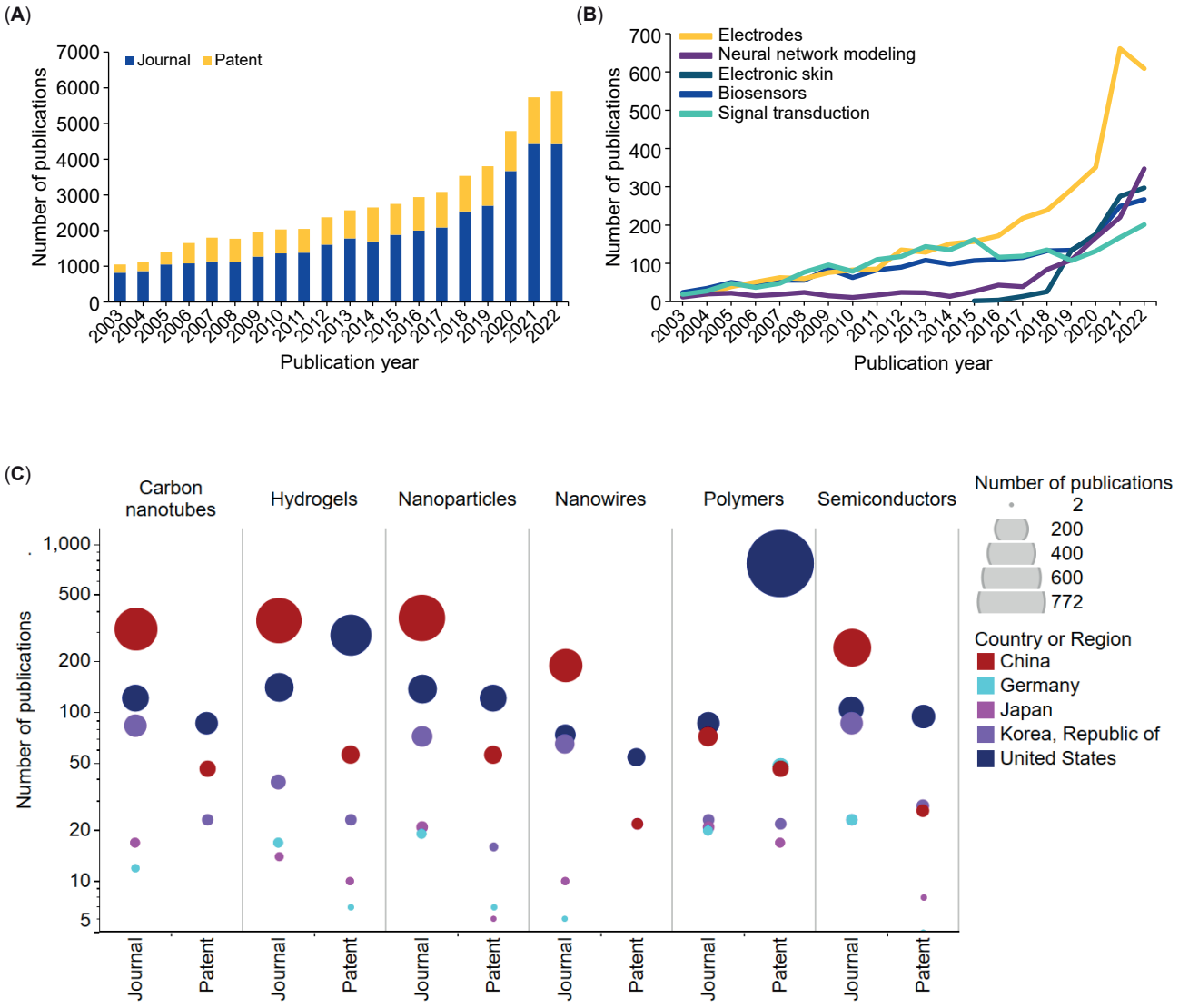


Figure 9. (**A**) Bioelectronic material-related publication trends journals and patents. (**B**) Publication trends based on emerging applications with the highest number of publications. (**C**) Publication trends in bioelectronic materials among the materials with high number of publications. The illustration shows the publication numbers in journals and patents among the top five countries with the overall highest number of publications from 2003 –2022.

X. Sustainable biomaterials

Approximately 9–13% of global solid waste consists of high molecular weight fossil-based plastics.[249] The packaging industry is the largest contributor to plastic waste worldwide.[250] Plastic, being a toxic and non-biodegradable pollutant, poses a threat to the environment, persisting in water and soil for extended periods and causing what is commonly known as "white pollution." Moreover, the release of chemicals used to enhance the properties of plastics further exacerbates its detrimental impact on living organisms' health. In the medical field, products like disposable masks, gloves, gowns, containers, packaging materials, and laboratory supplies such as cell culture dishes, pipet tips, and centrifuge tubes have also contributed significantly to environmental pollution. The COVID-19 pandemic has aggravated this situation owing to the increased usage of disposable personal protective equipment (PPE) like masks, gloves, and gowns. Therefore, there is a growing need to develop sustainable materials for PPE, and other medical and laboratory supplies, learning from the lessons of past pandemics.

The ideal replacement for conventional plastics would possess the following features: (1) sourced sustainably; (2) biodegradability in the environment; (3) economic viability for large-scale production and utilization; and (4) retainment of essential plastic characteristics such as durability and light weight. Over the past few decades, researchers have been exploring alternative materials that are less harmful to the environment and more sustainable in terms of resources to replace plastics. These materials can generally be classified based on their sources (bio-based or fossil fuel-based) and degradability (biodegradable or nonbiodegradable) (**Figure 10A**). In recent years, a new term, "bioplastics" has emerged to describe materials produced through biological processes, derived from renewable resources, or a combination of both. Some polymers that are both biodegradable and derived from fossil fuels are also referred to as "bioplastics".[251, 252] A drastic increase in the usage of this term has been noticed in journal publications (**Figure 10B**).

In recent years, many bio-based and biodegradable polymers with plastic-like functionalities have been extensively studied. **Figure 10C** depicts the total number of publications on these commonly studied polymers. Poly (lactic acid) (PLA), cellulose, starch, and chitosan have been the most researched materials in the last two decades. However, when considering the relative publication growth rate of each polymer, polybutylene adipate terephthalate (PBAT) and lignin have shown faster growth rates compared to others in the past five years (**Figure 10D**).

Given the increasing concerns of air pollutions and prevalence of diseases like COVID-19, the use of PPE has become increasingly common. To meet these high demands without burdening the environment further, biodegradable plastics are being seriously considered.[253] Biodegradable materials such as PLA, poly(lactic-co-glycolic acid) (PLGA), alginate, chitosan, gluten, and cellulose acetate also have gained renewed relevance as potential raw materials for producing disposable and degradable masks. Masks made from bio-based materials like PHA and biocellulose can effectively release active ingredients through the skin.[254, 255]

Finally, the importance of economic viability of plastic alternatives cannot be overstated. It is imperative that these new materials are not only environmentally friendly but also financially viable for manufacture setup, large-scale production, and utilization. By striking the right balance between sustainability and affordability, we can encourage widespread adoption and make a significant impact on reducing plastic waste globally.

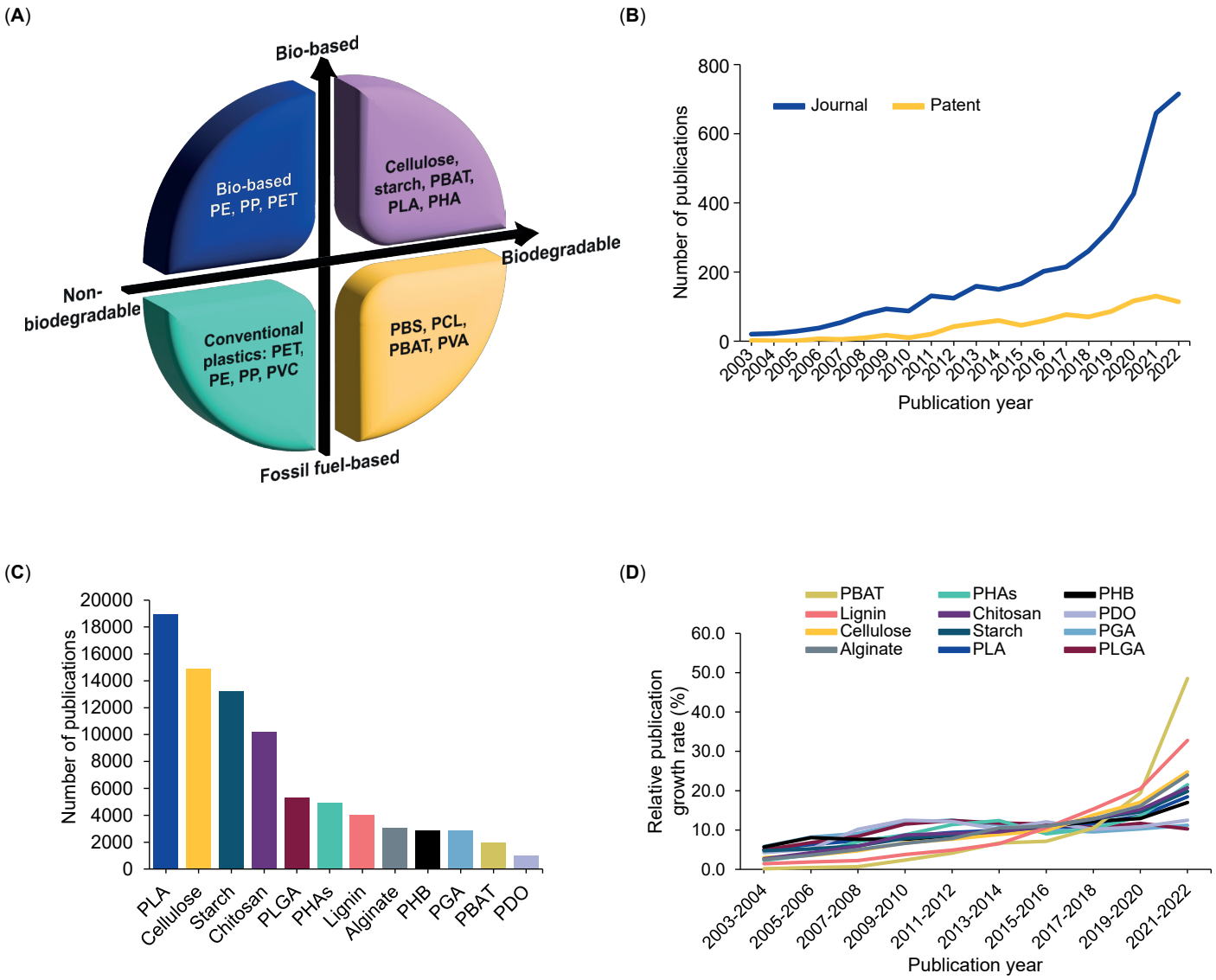


Figure 10. (**A**) Classification of natural and synthetic polymers based on their origin (bio and fossil-based) and biodegradability (biodegradable and non-biodegradable). Abbreviations: PE – polyethylene; PP – polypropylene; PET – polyethylene terephthalate; PBAT – poly (butylene adipate-co-terephthalate); PLA – poly (lactic acid); PHA – polyhydroxyalkanoate; PVC – polyvinyl chloride; PBS – polybutylene succinate; PCL – polycaprolactone; PBAT – poly (butylene adipate-co-terephthalate); PVA – polyvinyl alcohol. (**B**) Plots showing the annual numbers of journal and patent publications mentioning the term "bioplastics" (2003–2022). (**C**) Commonly seen bio-based and biodegradable polymers and their publication numbers from 2003 to 2022. Abbreviations: PLA – poly (lactic acid); PLGA – poly (lactic-co-glycolic acid); PHAS – polyhydroxyalkanoates; PHB – polyhydroxybutyrate; PGA – polyglycolic acid; PBAT – poly (butylene adipate-co-terephthalate); PDO – Polydioxanone. (**D**) Relative publication growth rates of commonly seen bio-based and biodegradable polymers (2003-2022).

Perspective

The field of biomaterials holds immense potential for advancing science and technology. Biomaterials have proven their worth in a wide range of applications, including medical implants, tissue healing, and regeneration. Moreover, their use extends to molecular probes, biosensors, and advanced drug delivery systems, showcasing the interdisciplinary nature of this field, requiring expertise in biology, chemistry, engineering, and medicine.

Commercial companies have recognized the significance of biomaterials, actively engaging in their development and application for innovative biomedical products. Through judicious exploration of structure-function relationships, biological innovation has been able to meet the evolving demands of various industries, propelling remarkable progress in biomaterials. Diverse fields such as biosensors, drug delivery systems, regenerative tissue engineering, immune engineering, medical devices and implants, and biodegradable materials are contributing to this transformative journey. Looking ahead, the biomaterial domain is poised for even greater heights, with cutting-edge innovations in automation, computing, and artificial intelligence (AI) on the horizon. These advancements hold the potential to reshape the landscape of biomaterials and drive unprecedented growth.

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