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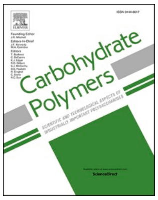

The European Polysaccharide Network of Excellence (EPNOE) research roadmap 2040: Advanced strategies for exploiting the vast potential of polysaccharides as renewable bioresources

Martin Gericke[a], Adérito J.R. Amaral[b], Tatiana Budtova[c], Pieter De Wever[d], Thomas Groth[e], Thomas Heinze[a], Herman Höfte[f], Anton Huber[g], Olli Ikkala[h], Janusz Kapuśniak[i], Rupert Kargl[j], João F. Mano[b], Már Másson[k], Pietro Matricardi[l], Bruno Medronho[m,n], Magnus Norgren[n], Tiina Nypelö[o,p], Laura Nyström[q], Anna Roig[r], Michael Sauer[s,1], Henk A. Schols[t], John van der Linden[u], Tanja M. Wrodnigg[j], Chunlin Xu[v], Gleb E. Yakubov[w], Karin Stana Kleinschek[j,*], Pedro Fardim[d]

[a] *Friedrich Schiller University of Jena, Institute of Organic Chemistry and Macromolecular Chemistry, Centre of Excellence for Polysaccharide Research, Humboldtstraße 10, D-07743 Jena, Germany*
[b] *Department of Chemistry, CICECO-Aveiro Institute of Materials, University of Aveiro, Campus Universitário de Santiago, 3810-193 Aveiro, Portugal*
[c] *MINES Paris, PSL University, CEMEF - Center for Materials Forming, UMR CNRS 7635, CS 10207, rue Claude Daunesse, 06904 Sophia Antipolis, France*
[d] *KU Leuven, Department of Chemical Engineering, Chemical and Biochemical Reactor Engineering and Safety (CREaS), Celestijnenlaan 200F, 3001 Leuven, Belgium*
[e] *Department Biomedical Materials, Institute of Pharmacy, Martin Luther University Halle-Wittenberg, 06099 Halle (Saale), Germany*
[f] *Université Paris-Saclay, INRAE, AgroParisTech, Institut Jean-Pierre Bourgin (IJPB), 78000 Versailles, France*
[g] *University Graz, Inst.f. Chem./PS&HC – Polysaccharides & Hydrocolloids, Heinrichstrasse 28, 8010 Graz, Austria*
[h] *Department of Applied Physics, Aalto University School of Science, FI-00076 Espoo, Finland*
[i] *Jan Dlugosz University in Czestochowa, Faculty of Science and Technology, Department of Dietetics and Food Studies, Waszyngtona 4/8, 42-200 Czestochowa, Poland*
[j] *Graz University of Technology, Institute of Chemistry and Technology of Biobased Systems, Stremayrgasse 9, A-8010 Graz, Austria*
[k] *Faculty of Pharmaceutical Sciences, School of Health Sciences, University of Iceland, Hofsvallagata 53, IS-107 Reykjavík, Iceland*
[l] *Sapienza University of Rome, Department of Drug Chemistry and Technologies, P.le A. Moro 5, 00185 Rome, Italy*
[m] *MED—Mediterranean Institute for Agriculture, Environment and Development, CHANGE–Global Change and Sustainability Institute, Faculdade de Ciências e Tecnologia, Universidade do Algarve, Campus de Gambelas, 8005-139 Faro, Portugal*
[n] *Surface and Colloid Engineering, FSCN Research Center, Mid Sweden University, SE-851 70 Sundsvall, Sweden*
[o] *Chalmers University of Technology, Department of Chemistry and Chemical Engineering, 41296 Gothenburg, Sweden*
[p] *Aalto University, Department of Bioproducts and Biosystems, 00076 Aalto, Finland*
[q] *ETH Zurich, Department of Health Sciences and Technology, Schmelzbergstrasse 9, 8092 Zurich, Switzerland*
[r] *Institute of Materials Science of Barcelona (ICMAB-CSIC), 08193 Bellaterra, Spain*
[s] *University of Natural Resources and Life Sciences, Vienna, Department of Biotechnology, Institute of Microbiology and Microbial Biotechnology, Muthgasse 18, 1190 Vienna, Austria*
[t] *Laboratory of Food Chemistry, Wageningen University and Research, Bornse Weilanden 9, 6708WG Wageningen, the Netherlands*
[u] *Becoming-Aware, D'Hoogvorstlaan 30, 1860 Meise, Belgium*
[v] *Åbo Akademi University, Laboratory of Natural Materials Technology, Henrikinkatu 2, Turku/Åbo, Finland*
[w] *Soft Matter Biomaterials and Biointerfaces, Food Structure and Biomaterials Group, School of Biosciences, University of Nottingham, Sutton Bonington LE12 5RD, United Kingdom*

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ABSTRACT

Polysaccharides are among the most abundant bioresources on earth and consequently need to play a pivotal role when addressing existential scientific challenges like climate change and the shift from fossil-based to sustainable biobased materials. The Research Roadmap 2040 of the European Polysaccharide Network of Excellence (EPNOE) provides an expert's view on how future research and development strategies need to evolve to fully exploit the vast potential of polysaccharides as renewable bioresources. It is addressed to academic researchers, companies, as well as policymakers and covers five strategic areas that are of great importance in the context of

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* Corresponding author.
E-mail address: karin.stanakleinschek@tugraz.at (K. Stana Kleinschek).

[1] Present address: OMV AG, Trabrennstr. 6-8, 1020 Vienna, Austria.

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polysaccharide related research: (I) Materials & Engineering, (II) Food & Nutrition, (III) Biomedical Applications, (IV) Chemistry, Biology & Physics, and (V) Skills & Education. Each section summarizes the state of research, identifies challenges that are currently faced, project achievements and developments that are expected in the upcoming 20 years, and finally provides outlines on how future research activities need to evolve.

1. Introduction

Polysaccharides are among the most abundant biological and renewable materials on our planet (Fig. 1). They are present in our everyday life in the form of energy storage, food, textiles, packaging, construction materials, and medicines. Polysaccharides will be central to the world of tomorrow as a transition to sustainable technologies is crucial for the future of humanity. Proper utilisation of polysaccharide resources has the potential to increase biodiversity, enhance food safety and sustainability, and decrease CO_2 emissions and pollution. Three main drivers strongly push the use of polysaccharides:

- the emergence of a bioeconomy that increases the contribution of biobased products
- the fact that these are polymers with various exceptional properties, opening routes for novel applications in all sectors of human activities such as materials science, nutrition, health, personal care, and energy
- the renewable character of polysaccharides, making them primary CO_2 neutral candidates for the global transformation to a more sustainable world.

To unfold the sustainable future of polysaccharides, a series of joint efforts in science, technology, education, and policy will be needed. The first step was already taken in 2007 when the European Polysaccharide Network of Excellence (EPNOE) Association was established with the support of the European Commission (EC). For 15 years, we have built a unique collaborative environment for scientists, institutions, and companies. Today, EPNOE is a vibrant organization with >50 institutions and companies from 20 countries. This unique international joint venture involving science, education and business inspired us to take the next step and create a visionary interdisciplinary document.

The EPNOE Research Roadmap presented herein is a joint collaborative effort of scientists from 13 European countries with the goal to build a unique vision of experts for the future of polysaccharide research and education in Europe and globally. The document has five strategic areas covering: (I) Materials & Engineering, (II) Food & Nutrition, (III) Biomedical Applications, (IV) Fundamental Sciences (i.e., Chemistry, Biology & Physics), and (V) Skills & Education.

1.1. About the European Polysaccharide Network of Excellence (EPNOE)

EPNOE (www.epnoe.eu) was established in May 2005 as a *Network of Excellence* with funding from the EC under the FP6-NMP program Grant Agreement ID: 500375. This network instrument was designed to reduce fragmentation and strengthen competitiveness by assembling a critical mass of resources and expertise centered on various fields of science and technology (in our case polysaccharides). The ambition for this network was to continue to exist and grow on a long-term basis. To reach this goal, EPNOE was registered as a non-profit association in December 2007 and continued its activities after the end of EC funding in October 2009.

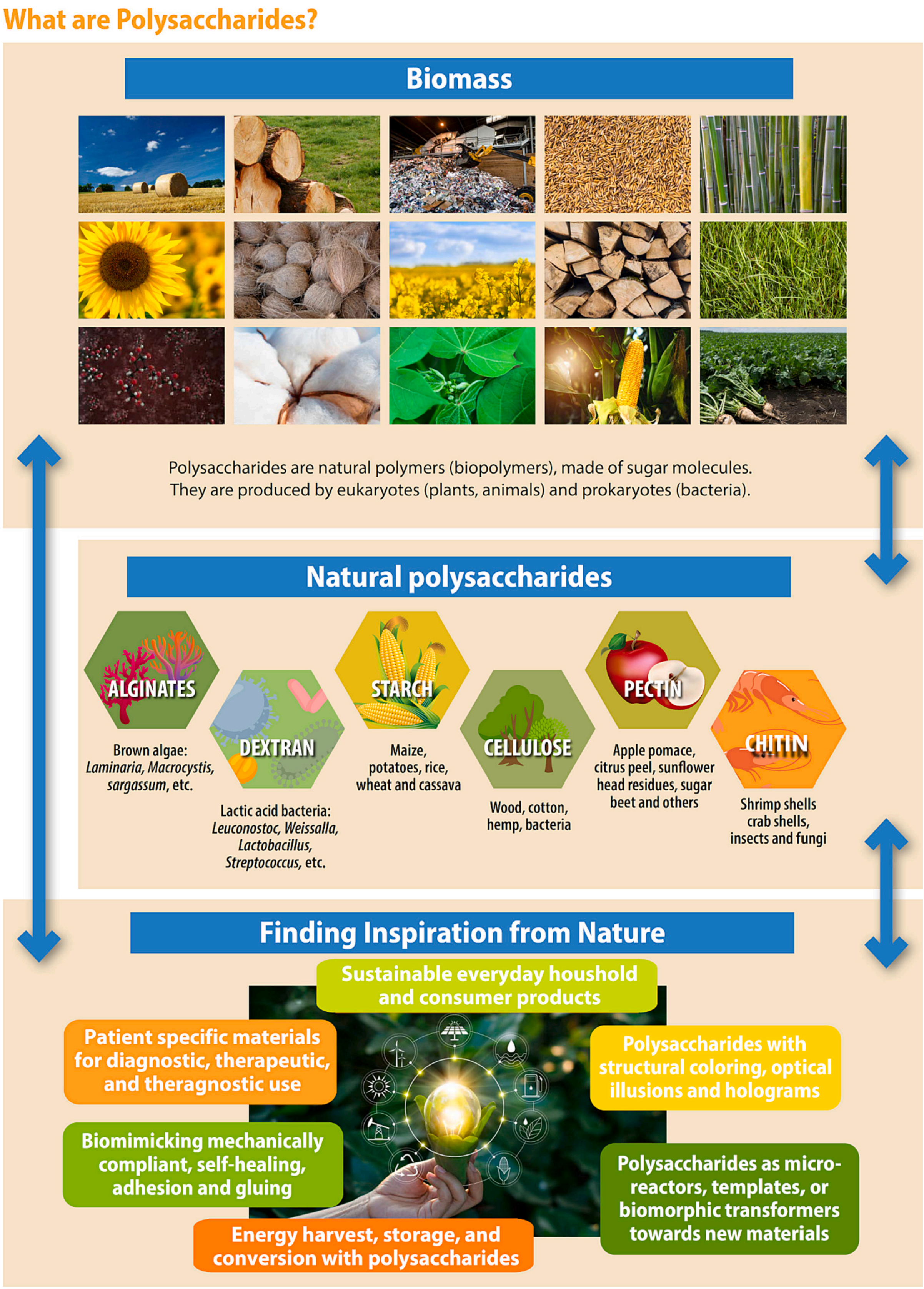
The initial focus of EPNOE was on promoting the use of polysaccharides as industry feedstock for the manufacturing of advanced, multifunctional materials. In March 2012, it received further funding from the EC for three years under the FP7-NMP program Grant Agreement ID: 290486 to expand activities towards health- and food-related materials and products as well as to increase industrial participation and innovation. EPNOE has continued after the end of the second period of EC funding in February 2015 and now sustains its activities from membership fees. The network, which began with 16 academic and research institutions from 9 European countries, has grown to include >50 academic, research and industry institutions from all around the world.

1.2. Polysaccharides and biomass in the global perspective

Polysaccharides are defined as polymeric compounds consisting of a large number of monosaccharides that are linked through glycosidic bonds (IUPAC, 1997). They are frequently also referred to as *glycans*. As such, polysaccharide research can be considered as part or extension of *glycoscience*, a branch of research that focusses on carbohydrates (mono-, oligo-, and polysaccharides) as well as assemblies of carbohydrates with other compounds such as proteins (Barchi, 2021; National Research Council Committee on Assessing the Importance and Impact of Glycomics and Glycosciences, 2012). Polysaccharides are produced in large quantities by plants but also by microorganisms and animals and are consequently considered as highly valuable renewable resources. It is accepted that the amounts of oil, coal, and gas that we have been using as our major energy sources since the industrial revolution cannot be easily substituted. Their use, however, impacts society, climate, and politics. It causes pollution, and is regarded as non-sustainable at the current rate of consumption. Fossil carbon use is complemented by our growing global consumption of biomass for food, energy, and materials (Krausmann et al., 2013). This biomass is, in turn, essential for the preservation of biodiversity, land, water resources, and human health. In any case, fossil carbon deposits and biomass are an integral part of the global carbon cycle. Solutions to the current instability of the climate system, to pollution, biodiversity loss, and to rising global demands must include the right treatment of fossil-based and bioresources.

Biomass and polysaccharides are seen as attractive resources because they are almost exclusively based on a fascinating circular mode of production of photosynthetically captured carbon dioxide, with water as the reductant. Despite the essential importance of biomass, the limited per capita amounts that are available with current technology and land-use schemes also cause controversies among scientists, policymakers, and the public about the role of biomass in mitigating global challenges (Bar-On, Phillips, & Milo, 2018). Concerns are raised that an ever-increasing industrial use of biogenic raw materials, and a growing demand for food, will lead to reduced biodiversity, destruction of ecosystems, and harm the global climate. Fig. 2 summarizes different opinions on the role and use of biomass in more sustainable economic systems as related to climate actions (Strengers & Elzenga, 2020). Strategies for prudent use of biomass and polysaccharides are therefore of utmost importance, and no simple solution exists. Significant research efforts are needed to understand biosynthesis, structural variations, material properties, and the influence of biomass on health, ecology, and societies. Furthermore, new technologies might be necessary to increase or modify biomass production and how it is produced, used, recycled, and discarded.

One of the objectives of the EPNOE Research Roadmap was to assess the availability of biomass (with a focus on polysaccharides) according to the current scientific literature. Annual terrestrial global



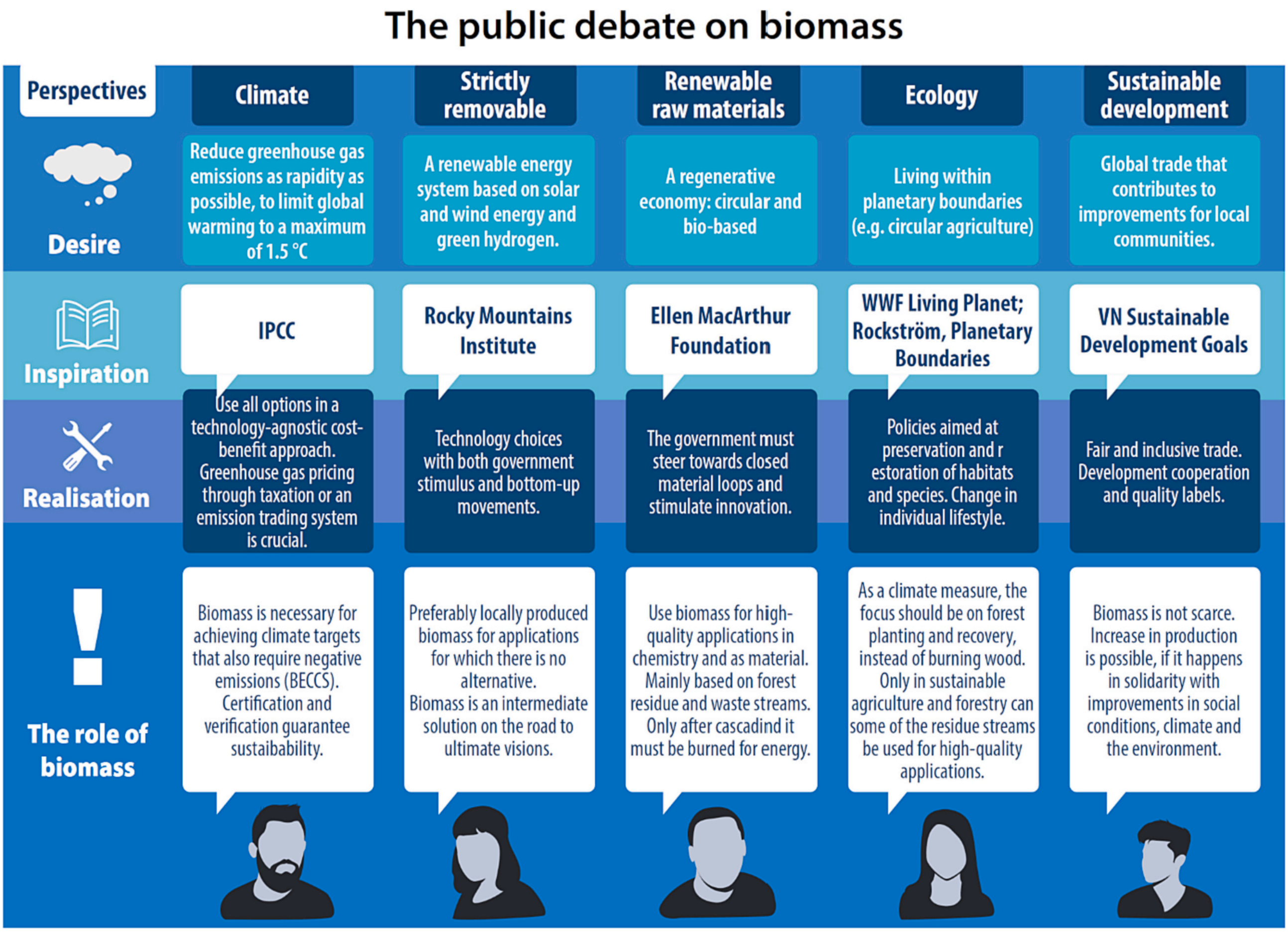
Polysaccharides are natural polymers (biopolymers), made of sugar molecules. They are produced by eukaryotes (plants, animals) and prokaryotes (bacteria).

Fig. 1. Schematic overview about the origin of some examples of polysaccharides and their role as biomass.

photosynthetic net primary production of biomass was estimated to be around 60 gigatons (Gt) of carbon (Beer et al., 2010; Haberl et al., 2007). It is projected that 8–10 Gt of carbon (i.e., approximately 1 t per capita)[2] are harvested each year by humanity in the form of biomass, with large regional disparities and increasing demands until 2050 (Zhou, Elshkaki, & Graedel, 2018). This has a significant impact on biodiversity, land, and other resource use. Compared to that, carbon emissions (in the form of CO_2) from fossil fuels and cement production were 9.5 Gt carbon in 2011, showing the magnitude of the disturbance of the natural biogenic carbon cycle by humans (Ciais et al., 2013). Although agriculture, forestry, and other land use are net CO_2 equivalent emitters (incl. CH_4, N_2O), it was assumed that the total global land area was a net sink of 11.2 ± 2.6 Gt CO_2 per year in the period 2007–2016 (Shukla et al., 2019). This demonstrates the enormous significance of biomass and polysaccharides in the context of the climate crisis.

According to recent studies, 1.466 Gt of dry matter biomass (ca. 3 t biomass per capita) was produced in 2013 by the land-based sectors in the European Union (EU, see Fig. 3), which back then encompassed 28 members states including the United Kingdom and Croatia. (Camia et al., 2018). The latest EU report (which excluded United Kingdom) describes a similar amount of approximately 1 Gt dry harvested biomass for 2017 (Avitabile et al., 2023). Other sources stated a photosynthetic net primary production of 2.335 Gt carbon per year in the EU (excluding Croatia; ca. 4.6 t carbon per capita), with 36 % of it being used by humans (Plutzar et al., 2016). It needs to be considered that “Not all the biomass produced is harvested and used, part of it remains in the field to maintain the carbon sink and the other ecosystem services” and that “The biomass harvested and used in 2013 from the EU agricultural and forestry sectors was estimated at 805 Mt dry matter (578 Mt from agriculture, 227 Mt from forestry)”. Biomass standing stocks are substantially larger, for example: “The total above ground woody biomass of EU-28 forests was estimated at 18 600 Mt of dry matter…” (Camia et al., 2018). According to these numbers and assuming that the current amounts are sustainably regrown, biomass and polysaccharides are a plentiful albeit not inexhaustible resource at the European level.

As shown in Fig. 4, harvested biomass is mostly used for the feed and food sector (60 %), followed by bioenergy (19.1 %) and biobased materials (”biomaterials”; 18.8 %) with the latter including forest products such as paper and pulp (Camia et al., 2018). Depletion of the productive biomass stock of Earth has to be avoided to keep the ecosystems intact. Thus, the use of biomass for energy, materials, or food has to be considered when balancing the net primary biomass production. Considerate implementation of the biogenic carbon cycle and the use of polysaccharides must therefore be a part of any sustainable circular economy. It follows that there is tremendous demand for research and development to understand and increase the sustainability of biomass production and use. It should also be pointed out that assessments



The public debate on biomass

Perspectives	Climate	Strictly removable	Renewable raw materials	Ecology	Sustainable development
Desire	Reduce greenhouse gas emissions as rapidity as possible, to limit global warming to a maximum of 1.5 °C	A renewable energy system based on solar and wind energy and green hydrogen.	A regenerative economy: circular and bio-based	Living within planetary boundaries (e.g. circular agriculture)	Global trade that contributes to improvements for local communities.
Inspiration	IPCC	Rocky Mountains Institute	Ellen MacArthur Foundation	WWF Living Planet; Rockström, Planetary Boundaries	VN Sustainable Development Goals
Realisation	Use all options in a technology-agnostic cost-benefit approach. Greenhouse gas pricing through taxation or an emission trading system is crucial.	Technology choices with both government stimulus and bottom-up movements.	The government must steer towards closed material loops and stimulate innovation.	Policies aimed at preservation and restoration of habitats and species. Change in individual lifestyle.	Fair and inclusive trade. Development cooperation and quality labels.
The role of biomass	Biomass is necessary for achieving climate targets that also require negative emissions (BECCS). Certification and verification guarantee sustaibability.	Preferably locally produced biomass for applications for which there is no alternative. Biomass is an intermediate solution on the road to ultimate visions.	Use biomass for high-quality applications in chemistry and as material. Mainly based on forest residue and waste streams. Only after cascadind it must be burned for energy.	As a climate measure, the focus should be on forest planting and recovery, instead of burning wood. Only in sustainable agriculture and forestry can some of the residue streams be used for high-quality applications.	Biomass is not scarce. Increase in production is possible, if it happens in solidarity with improvements in social conditions, climate and the environment.

Fig. 2. Schematic representation of examples of public debates with different opinions about the role of biomass (BECCS: Bioenergy with Carbon Capture and Storage Technologies; IPCC: Intergovernmental Panel on Climate Change; WWF: World Wide Fund For Nature; VN: United Nations).
Adapted from Strengers and Elzenga (2020) with permission.

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[2] Based on a world population of about 8.0 billion people in the year 2020 according to World Bank data. https://data.worldbank.org/indicator/SP.POP.TOTL.

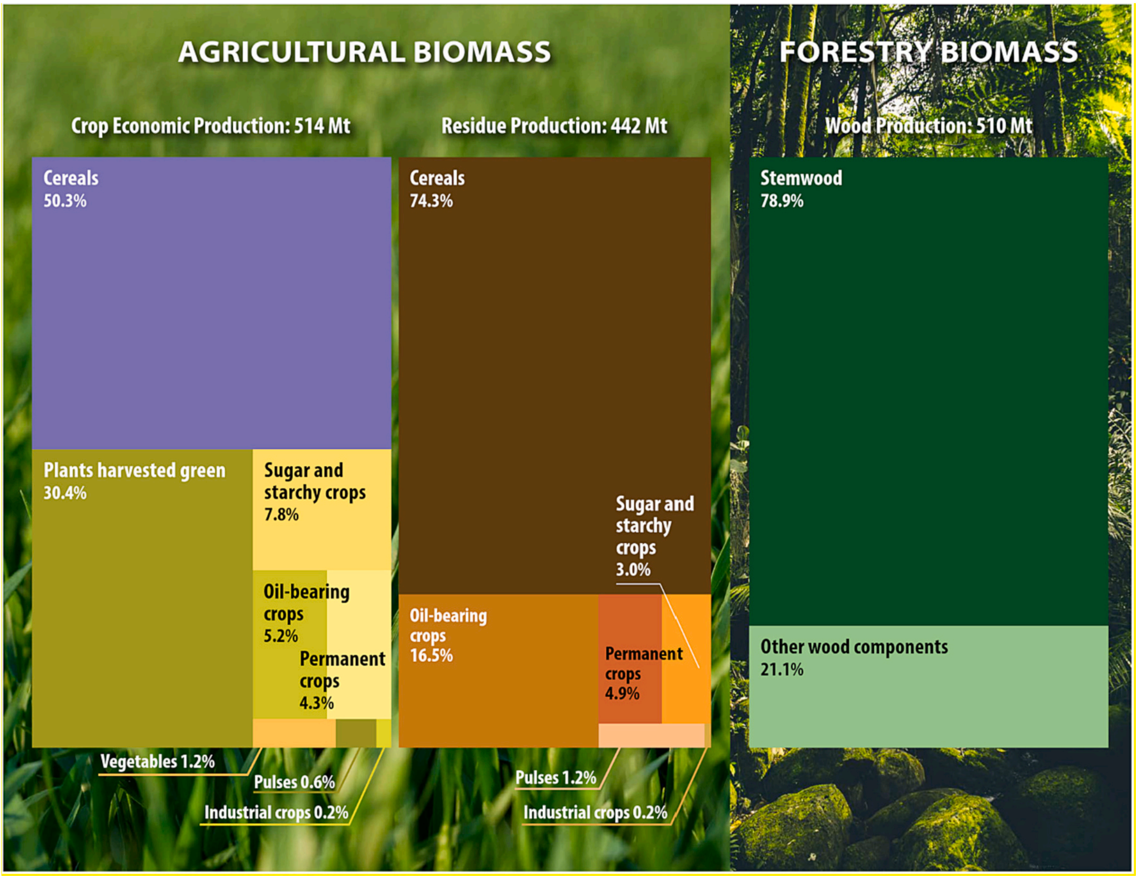

Fig. 3. Overview of the annual biomass production (in megatonnes (Mt) dry matter) from land-based sectors (excluding pastures) within the European Union (10-year average 2006–2015).
Adapted from Camia et al. (2018) with permission.

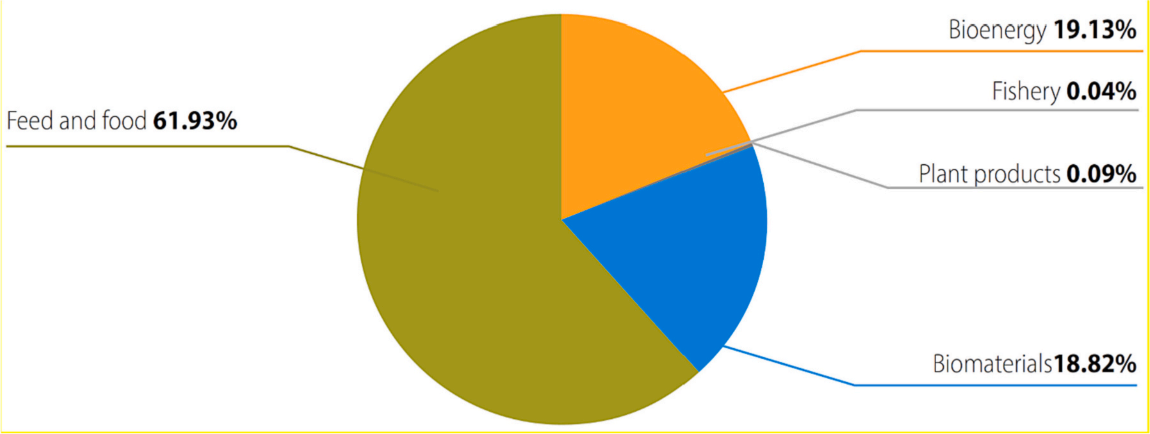

Fig. 4. Distribution of biomass uses in the European Union.
Adapted from Camia et al. (2018) with permission.

regarding to which extent biomass production and use can be called *sustainable* and with which technology biomass can substitute fossil carbon cannot be answered easily up to now. Moreover, gaps, uncertainties, and future developments for different biomass sources must be considered as described in the following quotes from literature (Camia et al., 2018):

- Biomass from agriculture: “However, it is important to note that food and feed uses are by far the main type of utilisation of agricultural biomass (in quantity). Being currently captured, the overall picture of agricultural biomass flows is already informative. Missing uses represent a very small fraction of agricultural biomass uses when measured in quantity, although they may represent a larger fraction of biomass uses when measured in economic value.”
- Biomass from forestry: “As already hinted at, there are numerous uncertainties in the data. The most critical concerns harvest levels and removals of woody biomass from EU forests. Another major

uncertainty relates to energy uses, values are often underestimated or at times outright missing."
- Biomass from fisheries and aquaculture: "With globalisation, international trade of seafood products has become very complex and seafood products can come from different sources, having often passed through various stations in the production and supply chain …. This poses many challenges to the already difficult monitoring activities in the whole fisheries sector." and "Potential environmental impacts of fisheries and aquaculture need to be assessed."
- Biomass from algae: "The FAO [comment: the Food and Agriculture Organization of the United Nations] and Eurostat databases include very fragmented information regarding the uses, economic value and market flows of algal biomass at the European level. This results from the incomplete reporting by member states and the confidentiality issues imposed by the business sector. Additionally, no information is available on the commercial use of algal biomass at national level. This limits the realistic assessment of the trade flows, for some species and countries with high internal market consumption of the biomass production." and "Resulting from market demands, global seaweed biomass production has increased exponentially in the last decade."

In addition to the mentioned facts, different scenarios should be considered, and sustainable biomass supply estimates need to be compared with models that project the demand and supply in 2040 and beyond.

2. The EPNOE Research Roadmap 2040

2.1. Concrete outreach to policymakers and key messages

The EPNOE Research Roadmap has strong and synergistic links to EU strategies and objectives, including the EU Bioeconomy Strategy, EU Green Deal, EU Missions, Horizon Europe Clusters, and EU Industrial Strategy. Polysaccharides are CO_2 neutral with additional advantages of acting as carbon storage, holding well-established processability at an industrial scale, and easy functionalisation to meet current and future challenges in commodity and speciality areas involving materials, energy, food, and health. These assets are of extremely high relevance when it comes to achieving the five goals of the EU Bioeconomy Strategy and climate neutrality of the EU Green Deal by 2050. Additionally, the advances in polysaccharide science and technology will open new frontiers required to meet the five EU Missions, to create new knowledge and innovation to successfully address opportunities in Horizon Europe Clusters and EU Industrial Strategy.

The following key messages are of outmost importance to fully understand the importance that polysaccharides will play in the future:

- Polysaccharides are essential to life, abundant, and tailored by nature to act as carbon storage and functionality carriers for essential areas of human and planet health and well-being. These features have been overlooked in National and European strategies.
- Sustainability and circularity require more emphasis on both the beginning and end-of-life scenarios of polysaccharide products. The end-of-life properties need to be designed at an early stage of research. Recyclability, biodegradability, reusability and, after cascading use, conversion to energy must be rationally designed and engineered from conception to production and include consumption and post-use.
- Polysaccharide innovations should aim for long-service life products to ensure and enhance carbon storage and functionality to replace fossil-based material solutions.
- Safety through the design of polysaccharide materials should be implemented in research and innovation policies to ensure that future solutions have minimal toxicity, are healthy for humans and the planet, and are economically, environmentally, and socially viable.
- Biomedical applications of polysaccharides should contemplate the manufacture and quality standards and scale of polysaccharide biomaterials from the research and development standpoint, their practicality, off-shelf use, cost-effectiveness, and business model. Moreover, the preparation of harmonised regulatory frameworks to accelerate the introduction of polysaccharide-based biomaterials into clinical practice in collaboration among academics, clinicians, companies, and regulatory authorities should be supported by policymakers.
- We suggest that consumers and citizens must be more engaged in polysaccharide-based solutions and informed about the advantages of polysaccharides and their benefits for the health of the planet, humans, and society. Development of labels, digital platforms, and tools to guide and support consumers and citizens with science-based knowledge is suggested.
- Cross-disciplinary collaborations need to be further supported with different stakeholders, including universities, research institutes, industry, non-governmental organisations, society, and all relevant players. Investments in fundamental science, in new analytical technologies to support the understanding of structure-property-relationships, in scaling up of research to support commercialisation, and in creation of new critical mass in circularity and replacement of plastics are required.
- Education and permanent training of polysaccharide scientists and technologists are essential to improve sustainability, circularity, and rational design of future processes and products. Education and training activities involving different stakeholders, disciplines, and societal actors need support at National and European levels. Co-creation workshops, training schools, joint degrees, policy briefs, innovation workshops with combined inputs of academics, small enterprises, industry, and policymakers are examples of activities to be further supported.

2.2. General outline and structure of the roadmap

The strategic EPNOE Research Roadmap covers different relevant areas (Fig. 5). The following document was prepared considering the broadness of the topic and the gaps and uncertainties of available literature and it is based on the knowledge and skills of experienced researchers working in the respective areas. The major areas that will impact polysaccharide-related research in the future are covered: (I) Materials & Engineering, (II) Food & Nutrition, (III) Biomedical Applications, (IV) Chemistry, Biology, & Physics, and (V) Skills & Education. Each individual paragraph will provide a discussion on (i) the current challenges, (ii) the expected achievements and developments in the coming 20 years, and (iii) the required research activities needed to address the most important scientific and societal questions to be answered. The main goal of the EPNOE Research Roadmap is to arrive at solutions for a sustainable use of biomass resources while enhancing biodiversity. The strategic choice of research activities in polysaccharides as a part of a very diverse biomass is very important and essential to achieve a sustainable development of our society.

3. Materials sciences & engineering

To date, most plastic man-made materials and their composites are made from fossil-based polymers. Their ability to be moulded with the desired shape, their durability, light weight, and inexpensive production have made plastics the most employed man-made material so far. In the context of a more sustainable planet and a more efficient circular economy, polysaccharides are very well-positioned to transition from fossil-based to biobased materials with equal or improved performances. The share of biobased materials in commodities and consumer and speciality products is expected to increase steadily in the following

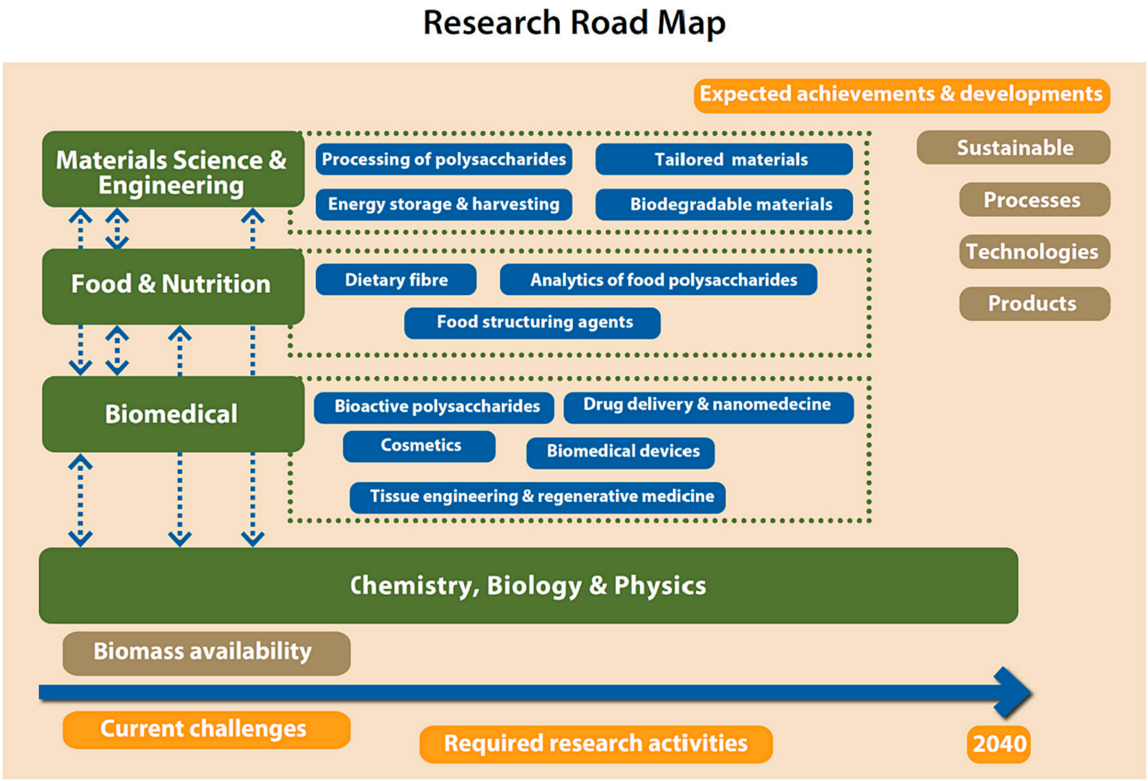

Fig. 5. Overall scheme of the EPNOE Research Roadmap with the key strategic scientific areas.

years. Below are some selected prospects for the next 20 years in terms of new tailor-made polysaccharide-based materials, their emerging applications and novel processing approaches.

(i) The next generations of polysaccharide-based materials will complement currently employed semi-synthetic materials and find inspiration in nature in the attempt to mimic both form and function:

- in polysaccharide derivatives that replicate bioinspired functionalities and low degrees of substitution as opposed to traditional polysaccharide esters and ethers used as thermoplastics and coatings
- in structural colouring in optoelectronic and photonic devices
- in bioimplants, biosensors, and biointegrateable electronics such as electronic eye and skin, wearable and implantable electronics as soft and deformable mechanical supports
- in bioactive polysaccharides that can generate novel materials

(ii) The use of functional composites from sustainable and renewable resources will be pivotal in our future industrial practices. Polysaccharides can be used both as a continuous or a dispersed phase:

- polysaccharide matrices with a magnetic, plasmonic, or conductive dispersed phase
- polysaccharide-protein interpenetrated networks for stiff and tough hydrogels
- transparent wood for touch-sensitive tactile panels
- biodegradable materials, in particular for packaging applications

(iii) Processing of polysaccharides must be economical and environmentally competitive:

- more efficient biorefinery approaches should be developed for extraction, purification, and shaping of polysaccharides
- methods already well-established in other areas but new in the context of processing of polysaccharides should be explored
- new sources of polysaccharides, such as microalgae, hemicelluloses, or exopolysaccharides (e.g., yeast-based, recombinant cell factories) have to be considered

(iv) The current increased digitalisation and continuous development in the area of *internet-of-things* must be combined with sustainable practices. Polysaccharides will thus be strategic components for energy storage and harvesting, replacing synthetic polymers:

- in batteries as binders, separators, and electrolytes
- in supercapacitors as biobased carbons, binders, dispersing agents, and permeable separators
- for energy harvesting, such as cellulose-based dielectric materials in triboelectric nanogenerators
- in solar cells, photonic and optoelectronic applications
- as flexible substrates in wearable electronics

Although polysaccharides might appear as an inexhaustible resource, it is important to identify and study the available feedstock in relation to the techno-economical perspective for each specific product and application to enable a sustainable production. Interdisciplinarity combined with the sustainable and circular economy should be a general approach to advance.

3.1. Next generation of polysaccharide-based materials and functional composites

3.1.1. Current challenges

Most fossil-based synthetic or semi-synthetic polymers are easy to shape, lightweight, and have a long-lasting exploitation duration. Their inexpensive production has made them one of the most employed materials during the past century, with a production of over 400 million tons in 2020, about 50 % more than in the previous decade. In the quest to transition from fossil-based to biobased materials with equal or improved performances, polysaccharides are well-positioned. To that end, polysaccharide-based materials with a higher degree of complexity and added value are gathering deserved growing scientific interest, aspiring to secure a place in high-tech sectors by demonstrating improved performance and functional versatility. However, polysaccharide alternatives for the replacement of oil-based plastics still have many challenges. Currently, the latter can be produced easily and cascaded down to energy recovery, while comparable technologies for polysaccharide-based solutions are still under development. Other relevant challenges are: "How much land will be needed?" and "What will be the environmental cost to produce the required biomass as raw material for polysaccharide-based plastics to replace oil-based ones?"

3.1.2. *Expected achievements and developments in the next 20 years*

Next generations of engineered polysaccharide-based materials will continue to be inspired by the animal-, plant-, and mineral kingdoms. The vision is to use natural models to guide material scientists to smartly select the right combination of polysaccharides and adequately process them to manufacture increasingly reliable natural replicates that could mimic both form and function (Heise et al., 2021). As an example, the panoply of optical phenomena found in nature as a result of complex light-harnessing and light-matter interaction will find replicates in nanostructured polysaccharides, i.e., materials with structural colour holograms, light waveguiding and control of transparency, haze or scattering centres (Droguet et al., 2022). Such materials will then be integrated into optoelectronics and photonic devices, and even the material will be designed to serve as a device. Bioinspiration, taken from skeletal-muscle tissues with highly oriented and densely packed myofibres to transmit forces and contract muscles or from the amazing regeneration potential of foetal skin involving the formation of actin cables at wound edges, will stimulate the creation of new polysaccharide-based materials that are mechanically compliant, stimuli-responsive, self-healable, or adhesive in wet bioenvironments (Blacklow et al., 2019).

Here, the expectations are that polysaccharides can play a key role in the future of bioimplants, biosensors, and biointegratable electronics (such as electronic eyes and wearable and implantable electronics) as soft and deformable mechanical supports that can efficiently dissipate the induced stresses from the body movement. In addition, wood, cellulose fibres, and other polysaccharides have tremendous potential for the fabrication of highly engineered materials and as templates to guide the fabrication of other materials (Li et al., 2021). Their hierarchical porous structure or the nanoscale size of the fibres will serve on a variety of templating mechanisms to obtain biomorphic structures. Finally, the field of engineered living materials to biosynthesise novel materials using cells is a futuristic vision to employ bioactive polysaccharides (Gilbert et al., 2021).

The increased use of composite biobased materials from sustainable and renewable resources is pivotal for the next generation of industrial practices (Mohanty, Vivekanandhan, Pin, & Misra, 2018). The polysaccharide component can act as the primary phase using a non-polysaccharide secondary component to endow functionality such as magnetic, plasmonic, electric, or ionic conductivity (Roig-Sanchez et al., 2019). Alternatively, the composite can be entirely manufactured with biopolymer components, i.e., by using polysaccharides and proteins conjoined networks strategies in the quest for stiff and tough hydrogels (Xu et al., 2019), or the use of nanocelluloses to improve gas barrier and sub-optimal mechanical characteristics of starch used in the food industry. Besides, synthetic polymers will be reinforced by wood or nanocelluloses (which is already produced on a large scale) and will play a role in fine-tuning the rheology of the polymer, impacting the capacity for 3D printing or UV-curing them. Engineering wood for technological applications deserves specific mention. A unique structure and anisotropy provide wood with opportunities beyond its structural function. For instance, after delignification, transparent wood can be obtained, resulting in a lightweight material with load-bearing properties that can encompass lighting features via the inclusion of luminescent particles (Montanari, Ogawa, Olsén, & Berglund, 2021). Besides construction industries, the automotive sector is highly interested in integrating electronics into touch-sensitive wood tactile dashboards.

The development of biodegradable packaging materials, particularly those based on polysaccharides, presents a promising opportunity for addressing environmental concerns associated with traditional packaging. For example, paper-based packaging based on lignocellulosic fibres already share 25 % of the packaging market and is expected to grow annually at the level of 4.7 % during 2023–2028.[3] In addition to their natural biodegradability, several polysaccharides such as cellulose and starch possess excellent film-forming properties (Cheng et al., 2021). Blending of polysaccharides and/or making composite materials (e.g., with starch or nanocellulose) allows the fabrication of intelligent packaging with tuneable mechanical-, barrier-, and/or antimicrobial properties (Wu, Misra, & Mohanty, 2021; Zhong, Godwin, Jin, & Xiao, 2020). Smart packaging solutions should go beyond traditional roles, offering real-time data and interactive features that enhance product safety, quality, and consumer engagement.

3.1.3. *Required research activities*

From a materials science viewpoint, to fully display polysaccharides' opportunities in materials and engineering, research activities will be necessary for a wide span of different areas. The use of advanced characterisation tools as well as computational and machine learning approaches to inform on potential new designs and assist in the understanding of the structure-property-relationships of the novel engineered polysaccharides will be necessary.

Other required research activities will be more specific to the type of material being developed and its final application. For instance, although, at present, 100 % polysaccharide-based materials have a sizeable market share in sustainable and biodegradable packaging, more research efforts are needed to increase their durability, lower their costs, and tune their properties towards specific applications (e.g., food industry). In the context of functional nanocomposites, significant challenges are in the development of high-strength nanocomposites with exquisite control and reproducibility of the nanoparticles' properties, their loading fraction and topographic distribution within the polysaccharide matrix. In addition, large-scale fabrication processes and success stories of their commercial use will have to be ensured.

Concerning biomaterials, meaningful research activities could focus on the control of self-degradation or trigger-able detachment of biointegratable implants for minimally invasive surgeries, the decrease of cross-linking reagents and decrease or avoidance of non-polysaccharide components in hybrid nanocomposites, as well as in the finer tuning and modelling of material responsiveness to various stimuli or the implementation of a self-regulative function considering the continuous diffusion between the tissue and the biomaterial. To impact the light/polysaccharides interactions, a precise control of transparency, degree of haze, modulation of structural colours, and precise waveguiding will be important for optoelectronic applications. Achieving the formation of holograms using polysaccharide building blocks will certainly be a major accomplishment in the field.

In the developing field of engineered living materials, the biosynthesis of polysaccharides with predictable and complex 3D architectures and functions across multiple scales in a continuous production loop will be a major research topic in the coming years. Finally, the use of polysaccharides in microfluidics for single-use recyclable devices is rapidly growing, while their use in transient electronics, an emerging class of electronics programmed to dissolve within a period of time without

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[3] Paper Packaging Market Size & Share Analysis - Growth Trends & Forecasts (2023–2028); source: https://www.mordorintelligence.com/industry-reports/paper-packaging-market.

generating harmful by-products, is a stimulating research field expected to capture enormous interest in the coming years.

3.2. Processing of polysaccharides

3.2.1. Current challenges

Processing is defined as transforming raw materials into finished products of certain shapes and properties. Polysaccharides are polymers; however, not all processing approaches developed for synthetic polymers can be and are currently used. Most polysaccharides are not thermoplastic. The difficulty in shaping polysaccharides results, in part, from strong intra- and intermolecular interactions between macromolecules, which prevent chains' mobility needed for melt processing.

The majority of natural polysaccharides are thus processed via solubilisation. Depending on the application, many of them remain in a dissolved state: for example, pectin, alginate, and carrageenans are used as viscosity modifiers, gelling agents, and gels in food, cosmetics, and pharmaceutics. These polymers can also be shaped into films by casting solutions followed by solvent evaporation. Cellulose dissolved via the viscose process is spun into fibres for textile and non-woven applications or cast into films. Much progress has been made in finding cellulose dissolution options (Lyocell process, dissolution in ionic liquids) as an alternative to the viscose process, which is very polluting (Liebert, 2010). Chitin is very difficult to dissolve and it is thus transformed into chitosan, which can then be dissolved in acidic aqueous media and processed into fibres or films (Pillai, Paul, & Sharma, 2009). To use starch for food applications and for packaging, it is usually prepared as an aqueous paste, which is the result of a gelatinisation process (Wang & Copeland, 2013). Foams and films are made from thermoplastic starch for packaging and agricultural applications.

The above concerns the processing of neat polysaccharides. However, except in very rare cases, polysaccharides exist in nature as mixtures with various other substances of low or high molecular weight. The classical example is natural fibres which are complex composite materials of polysaccharides (cellulose and hemicelluloses) and non-polysaccharide polymers (lignin) organised in a sort of an interpenetrated network. Alginate or carrageenan in seaweeds coexist with cellulose, proteins, minerals, and lipids. Chitin in crustacean shells or in mushrooms is mixed with minerals and proteins. Extraction of polysaccharides from these natural composites is thus needed for their further processing. The extraction methods are well known, but optimisation is still needed to improve efficiency and decrease the use of harmful chemicals.

Polysaccharides can also be processed in suspension after extraction or disassembly of native polysaccharide particles and fibrils from biomass. This process involves multiple steps, and it is resource and energy intensive. Finally, chemically modified polysaccharides, so-called polysaccharide derivatives, make a class of polymers with some of them being thermoplastics or easy to dissolve in water (e.g., cellulose ethers). Several cellulose esters can be melt processed in the same way as synthetic polymers. They can also be dissolved to cast films and spin fibres and non-wovens. Starch derivatives are processed and used in a similar way as cellulose derivatives.

Microorganisms as cell factories play several roles in the context of polysaccharide chemistry and processing (Tiwari, Sasmal, Kataria, & Devi, 2020). Many bacteria produce exopolysaccharides, which are industrially quite important, such as xanthan. Other polysaccharides produced by microbes (such as hyaluronic acid, kefiran, or gellan) are currently used for biomedical applications (Mohd Nadzir, Nurhayati, Idris, & Nguyen, 2021). Bacterial cellulose is of special importance for biomedical applications due to its high purity. Its properties can be modified by varying the cell factory or the production conditions, opening new fields of cellulose chemistry, processing, and applications. Levans are of increasing interest; they are fructans of bacterial origin with quite interesting properties. Microorganisms are also producing polysaccharide-modifying enzymes and can thus be used as whole cell catalysts for polysaccharide modifications. As such, microbial catalysts open new opportunities for polysaccharide chemistry and processing.

3.2.2. Expected achievements and developments in the next 20 years

Biorefinery approaches are and will be in the focus of polysaccharide processing: their extraction, purification and shaping. New processing methods (in the context of polysaccharides) have begun to be applied. The management of resources must be sustainable, and their use must be efficient, with minimum waste, and environmentally friendly. This requires reconsideration of the traditional ways of polysaccharide processing, which opens prospects for innovation. For example, new eco-friendly solvents and their recovery are a focus of research. This concerns cellulose dissolution and shaping, which is an old but still a very relevant problem. Some ionic liquids have been demonstrated to be powerful cellulose solvents, and the properties of fibres spun from these solvents compete with those obtained from viscose and Lyocell processes (Hummel et al., 2016). Still, ionic liquids are expensive, and to date, their recovery is complicated. There is a revival of interest in aqueous hydroxide-based solvents to be used for cellulose shaping (Budtova & Navard, 2016). Research on cellulose eco-friendly dissolution and shaping will continue to be an important topic.

Several methods that have never been used for polysaccharides are find increasing consideration. This leads to the creation of new materials with novel and unexpected (for polysaccharides) properties. For example, *bio-aerogels*, obtained from gels using drying under supercritical conditions, are new materials born at the beginning of the 21st century (Zhao, Malfait, Guerrero-Alburquerque, Koebel, & Nyström, 2018). A deeper understanding of the fundamental principles of the processing technologies in the context of polysaccharide research will yield novel biobased materials with unique properties and fields of application.

Additive manufacturing for shaping non-melting polysaccharides will be developed. 3D printing of thermoplastics, mainly synthetic polymers, is now reasonably well explored. Printing of polysaccharide solutions involves other mechanisms of shape stabilisation. Bioprinting can underpin new biomedical applications (e.g., tailormade scaffolds hosting cells and bioactive agents for tissue engineering). We are now only at the beginning of a long, explorative way.

New or not previously used sources of polysaccharides are now under investigation in the view of a biorefinery approach. Microalgae, which have been considered mainly as a source of biofuels, are also a promising sustainable feedstock containing polysaccharides. Extraction and separation of polysaccharides require new approaches and the development of novel technologies such as, for example, filtration systems for fractionation. Until recently, hemicelluloses have been regarded as a waste, when they could, instead, be used for the production of chemicals (e.g., furfural), biooils, or second-generation feedstock for fermentation. The diversity of known microbial species is constantly increasing. New exopolysaccharides are, for example, yeast-based. Many of them have peculiar biochemical or physical properties, which allow the development of new applications (Rahbar Saadat, Yari Khosroushahi, & Pourghassem Gargari, 2021). Efforts are ongoing to establish recombinant cell factories for agar (and other natural polysaccharides) production to satisfy the current market and enable new applications. One possibility to decrease waste and environmental impact is to produce less refined products and make use of the physical properties of these products. It is not always required to go to high purity; on the contrary, lower purity can even lead to products with improved properties compared to pure products. This approach opens opportunities for new applications with fewer processing steps.

3.2.3. Required research activities

One of the general approaches to be taken is interdisciplinarity. As polysaccharides are now considered in applications that were not even imagined 10–20 years ago, new (for polysaccharides) processing methods should be used and adapted to these applications.

Collaboration with researchers from other disciplines will be the way to advance. Another important aspect of processing is to use the sustainable and circular economy approaches.

The composite approach in polysaccharides will be more widely used, i.e., mixing polysaccharides with various organic or inorganic substances. Miscibility, dispersion, and distribution of the filler, compatibilisation (or not), filler transformation during mixing, biopolymer blends, and development of morphology during processing will have to be considered and adjusted according to the targeted application.

Processes for making polysaccharide materials with tuned morphology, such as porous polysaccharides, will continue to be developed. Drying methods as a part of processing will be in the focus as they control the porosity and morphology of the final material. Existing approaches should be coupled with specific polysaccharide functionalisation.

A deeper - and above all - systematic analysis of exopolysaccharides from newly identified microorganisms will be required to gain access to so far untapped natural resources. Of particular importance is the analysis and control of the biosynthesis of polysaccharides by microorganisms – the current knowledge is, in many cases, limited. Often peculiar sugars are required in biochemically activated form for the synthesis of polysaccharides. The mechanisms of how a polysaccharide is produced and transported to the extracellular space is often unclear. Finally, the special properties of the polysaccharides often derive from specific modifications (such as pyruvylation, sulfation and many more). Detailed knowledge about the mechanisms of biosynthesis and the involved enzymes would allow us to rationally design polysaccharides by metabolic engineering. A close collaboration of biochemists, molecular biologists, and industrial microbiologists will bring microbial polysaccharide production to a new level. Developments in the field of synthetic biology can contribute to designing and developing these tailormade new products.

3.3. Emerging polysaccharide applications in electric energy storage and harvesting

3.3.1. Current challenges

Electric energy supply and utilisation are essential for the functioning of the society. In May 2021, the International Energy Agency IEA released its roadmap to global net-zero emissions, analysing the implications of existing net zero pledges and showing a pathway to achieving net-zero emissions in electric energy production globally by 2050. In connection to this, a tremendous annual increase in off-grid electric energy storage and distribution is already appearing. Materials' solutions that can contribute to CO_2 reduction, as with many other aspects of sustainability, are getting increased attention scientifically and technically. In this respect, polysaccharides have shown promising performance and are foreseen to play an increasingly important role as components with multifaceted functionalities in electronics and energy materials in the coming decades (Zhao et al., 2021).

3.3.2. Expected achievements and developments in the next 20 years

In the next 20 years, distributed electric energy systems will continue to grow in importance. Besides the emerging need for off-grid storage in the electric power industry to efficiently balance the intermittent production output from wind and solar power generation, the electrification of the automotive sector and the increased digitalisation and continuous development in the area of internet-of-things will be the main drivers (Schlemmer, Selinger, Hobisch, & Spirk, 2021). In the development of batteries and supercapacitors, it can be expected that fossil-derived fully synthetic polymer materials will be continuously replaced with renewable polymers (Pérez-Madrigal, Edo, & Alemán, 2016). Carboxymethyl cellulose can be used as a binder, capable of compensating the volume change while maintaining stable performance and possibly exhibit self-healing. Also, other cellulose derivatives, alginate, gum arabic, xanthan gum, and chitosan, have shown to be promising binders. Nanopaper from cellulose nanofibrils has been applied successfully as separators in batteries, and further development is expected (Jabbour, Bongiovanni, Chaussy, Gerbaldi, & Beneventi, 2013). Moreover, polymer electrolytes in the form of gels and solids are well-suited components in certain battery applications. Different cellulose derivatives, chitosan, and algal-based polysaccharides have shown to be alternatives to conventional synthetic polymer electrolytes. This relatively new field is expected to gain in importance.

Supercapacitors are considered as one of the potential candidates in the domain of energy storage devices for future generations. There is a variety of applications covering large application areas; excess energy storage, powering electric vehicles, replacing batteries in electronics, as well as balancing the grid from fluctuations that arise in solar and wind power generation. Supercapacitors have generated great interest due to their higher power density, longer cycle lifetime and faster charge-discharge rate than batteries (Pushparaj et al., 2007). The electrodes often consist of carbon material, e.g., graphene or carbon nanotubes, as active materials and binders. Here, cellulose fibrils have been proven very suitable as binders as well as dispersion agents without decreasing the electrical performance. Cellulose nanofibrils and paper used as permeable separators that facilitate ion transport in charging and discharging, are also showing promising results (Nyholm, Nyström, Mihranyan, & Strømme, 2011).

Small-scale electronics are booming for the internet-of-things, wireless sensor networks, smart city design, and medical applications. The components of such devices typically require minimal amounts of power, but this becomes challenging when considering a large network of devices numbering in the billions. Maintenance costs will explode as the number of distributed micro-electronics increases, considering solutions where batteries must be replaced. Recent efforts to develop new types of energy harvesting systems, such as triboelectric nanogenerators, are therefore expected to ascend (Wu, Wang, Ding, Guo, & Wang, 2019). Owing to their attractive attributes, triboelectric nanogenerators have been successfully applied for harvesting all kinds of insignificant but abundant mechanical energy, such as vibrations, human body motion, wind power, and water motion. In this context, electrical insulating materials (dielectric materials) are necessary and superior. The reported performance profiles of cellulose, cellulose derivatives, and other polysaccharides in triboelectric nanogenerator applications are encouraging (Torres & De-la-Torre, 2021; Zhang et al., 2020). Future development is expected in many different real-world applications, where for instance, supercapacitors also can be included, realising battery-less internet-of-things solutions for sensing and monitoring. Moreover, polysaccharide materials can find their place due to their low toxicity and sufficient durability-(bio)degradability performance. Self-sufficient, fully green, and even transient (i.e., degrading in a controlled way in a biological environment), system solutions could be constructed in the future when combining these technologies.

A more sophisticated utilisation of paper is also expected. A practical approach for producing electronic devices on any flexible substrate is transfer technologies, which are currently a hot topic in wearable electronics platforms. There are already several types of transfer technologies available where all cell layers are initially deposited on a standard donor substrate (e.g., silicon) and after that they are transferred to the receiver substrate (i.e., speciality paper sheets). Fully printed solar cells on speciality paper substrates can also be realised for large-scale applications. Polysaccharide-based materials can be used in photonic applications (Ha, Fang, & Zhitenev, 2018). Photonic crystals enable a host of practical applications such as nonlinear waveguides, advanced anti-counterfeiting structures, and low-energy-consuming displays. Since structured cellulose-based composites exhibit high reflectivity, tuneable within the visible and near-infrared regions of the optical spectrum, applications ranging from colour filters to smart clothing designs and solar-gain-regulating building technologies can be expected. Cellulose-based materials can be designed for either cold or hot climates without compromising visible-range optical transparency. The use of cellulose in organic light-emitting diodes is another exciting application of polysaccharides in optoelectronic devices that will move forward.

3.3.3. Required research activities

In batteries and supercapacitors, the choice of electrolytes influences the stability of polysaccharides as binders and could also influence the properties of the membranes. More knowledge is needed to enhance future development.

Triboelectric research in the area of polysaccharides is still in its infancy. For instance, cellulose has several polymorphs that could influence the polarisation differently. Generally, an increased fundamental understanding of what is regulating the materials' triboelectric power output is needed, as well as how the performance can be optimised by different chemical and physical modifications. In transient electronics, an increased knowledge accumulation on how to control self-degradation is needed and can be expected.

At present, to use cellulose-based substrates in photovoltaic applications, several critical technological challenges need to be overcome to assure their performance and reproducibility. In this regard, several technical requirements such as thermal stability, mechanical properties, surface smoothness, high optical transparency and haze, as well as water barrier properties, need to be developed further.

From several viewpoints, forest-based polysaccharides might appear as inexhaustible biomass resources that could be utilised to solve almost everything. However, considering the whole system, it is evident that prioritizations will be necessary to fulfil sustainability requirements. As an example, in the production of nanofibres and cellulose derivatives to be used in the mentioned applications in this sub-sections, utilisation of many kinds of forest-based, agro-based and marine raw materials of lower quality than usual can be foreseen. This should be compared with the rather high demands on, for instance, the macro-fibre quality when producing pulps used for conventional and speciality paper-based products. From interdisciplinary perspectives, this makes it important and highly relevant to clearly identify and study feasible feedstocks other than wood, and from techno-economical perspectives, outline how to enable sustainable production.

4. Food & nutrition

Polysaccharides play a pivotal role in human nutrition and food structure design. Starches, being the major source of nutritional carbohydrates, were and remain to this date the prime focus of food research efforts. However, the last two decades saw a growing interest in complex oligosaccharides and polysaccharides and their assemblies that are not digestible by human enzymes. These types of carbohydrate materials are classified using the umbrella term *dietary fibre*.

Dietary fibre influence macronutrient digestibility and impact systemic, whole-body metabolism through a chain of physiological and metabolic events (Hoyles et al., 2018). These events begin with delayed gastric emptying, followed by the modulation of macronutrient digestion, and proceed to colonic fermentation of dietary fibre by the gut microbiome. At this point, fermentation-derived metabolites may enter the systemic circulation and plug into human metabolic pathways. Despite overwhelming epidemiological evidence supporting the link between dietary fibre intake and positive health outcomes, the intake of dietary fibre remains low across Western and Westernised diets (Hoyles et al., 2018).

Several research avenues have been pursued to tackle this challenge, including (i) identifying precise and specific physiological functionalities of dietary fibre, (ii) linking molecular and microstructure with functional properties, and (iii) developing new and enhancing existing fibre processing methods and techniques for their incorporation into food formulations. Conversely, new analytical and fibre characterisation techniques have become key enabling capabilities that underpin future advances, due to the complex and heterogeneous nature of carbohydrate structures. This roadmap identified several areas that will likely see substantial advances, including:

- in-depth evaluation of the nutritional, physiological, and technological properties of fibre polysaccharides and prebiotic oligosaccharides in complex food matrices
- improved understanding of the structure and composition of individual fibre polysaccharides and their complex assemblies
- mapping and monitoring dietary fibre transformation during fermentation, as well as uncovering the structural and dynamic interactions governing fermentation, resulting metabolites and mucosal interactions
- understanding chemical interactions between fibres and other nutrients and ingredients, such as proteins, fats, minerals, bile acids, and small bioactive molecules
- precision modification and transformation processes rooted in the in-depth understanding of fibre structure, from individual complex molecules to complex microstructures
- development of next-generation less-processed ingredients from upcycled and valorised side streams
- implementation of highly accurate, high-throughput, and high-speed characterisation methods
- polysaccharide sequencing through chemical and enzymatic fingerprinting to allow the distinction of polysaccharides with different patterns of substitution
- utilisation of highly advanced imaging techniques for characterising intact tissues and food products, including super-resolution microscopy, NMR imaging, and imaging mass spectrometry (MS)
- development of dedicated methods for the specific extraction of well-defined polysaccharides from inaccessible and insoluble matrices using physical techniques and environmentally friendly solvents

Within the strategic horizon of the next two decades, a more detailed understanding of the structural characteristics and structure-function-relationships of dietary fibre will enable the development of targeted dietary fibre polysaccharides with programmable interactions, rheological properties (gelling, viscosity), physiological responses (fermentability, immune modulation), as well as techno-functional properties to benefit public health, boost food system resilience, and achieve sustainable food processing and manufacturing. Taking a broader perspective, the goal is to ensure that consumers trust their food, the food is affordable, and the food journey from *farm-to-fork* is transparent.

4.1. Dietary fibre

4.1.1. Current challenges

Significant achievements of the past few decades saw a marked increase in the level of insight into the digestibility and fermentability of naturally occurring dietary fibre. In addition, there has been significant progress in exploring the functional capabilities of various fibre ingredients, including their roles as structuring-, gelling-, or thickening agents in technological applications.

Currently, dietary fibre reported on food package labels is referred to as *total dietary fibre* without specifying its functionality. There are several definitions for dietary fibre that specify the ingredients included in the total sum of fibre polysaccharides and, perhaps even more importantly, those that are not. From a polysaccharide perspective, it is generally important to identify fibre polysaccharides that are part of the total dietary fibre per the current definition. Even more crucially, it is important to specify, at the very minimum, the proportions of soluble and insoluble dietary fibre. Ideally, even more detailed aspects of the fibre structure should be considered, as they directly impact fermentability and interactions with other components in both the food and the gut. Only well-characterised fibre polysaccharides will allow for meaningful comparisons in the discussion on fibre functionalities and properties (Gidley & Yakubov, 2019).

In the current state of the matter, dietary fibre in the studies are primarily classified as soluble or insoluble – a factor that indirectly describes the length as well as the level of internal hierarchical structures between the individual polysaccharide types that may govern the interactions between individual fibre molecules. Fibre solubility is directly associated with the capacity of fibres to form physical structures and networks that enhance bonding between fibre chains. Insoluble fibre ranges from dense and weakly hydrated brans to complex gel-like cell wall structures (Gartaula et al., 2018). In these structures, the cellulosic nano- and micro-fibrils are surrounded by a hydrated matrix of hemicelluloses and pectins, forming complex structures of physically and partially tethered or cross-linked gels. Fermentability of insoluble fibre is highly dependable on the degree of cross-linking of non-cellulosic components and their structural complexity (Harris et al., 2023). On the other end of the spectrum, we find soluble fibre that are more readily fermentable by the intestinal microbiota owing to the better accessibility of the soluble fibre as a substrate for fermentation compared to its high molecular weight and insoluble counterpart. This connection between fibre structure and fermentability is very well established for individual fibre types but still insufficiently understood at the level of fibre mixtures and complex microbial populations that are dynamically changing and vary significantly between individuals (Makki, Deehan, Walter, & Bäckhed, 2018). Furthermore, the interactions of dietary fibre with small nutritionally relevant molecules, which may govern the availability of various nutrients, remain insufficiently understood. Similarly, understanding of the direct impact of fibre on immune cells has been demonstrated for certain fibre types, but systematic studies on this topic are still lacking (Beukema, Faas, & de Vos, 2020).

4.1.2. Expected achievements and developments in the next 20 years

The next two decades can be expected to proceed towards more in-depth research in dietary fibre polysaccharides towards a more detailed understanding of their structural characteristics and their features in terms of nutritional and technological activities in the complex food matrices. A key aspect to address will be to gain a better understanding of the structure-function-relationships of various individual fibre polysaccharides, i.e., the various chemical species of molecules, instead of the soluble *vs.* insoluble fractions as the type of fibre may have a larger impact on the effect than the overall intake (Thomson, Garcia, & Edwards, 2021). The past decades of research have demonstrated that in addition to the total dietary fibre content, it is essential to measure the proportions of soluble and insoluble fractions due to their specific nutritional and technological properties. Yet, the research in the past years has also shown that even more detail in the fibre characterisation is needed, especially for the soluble fibre fraction, as the functionality of the fibre is dependent on the solubility, molecular weight, fine structure, branching and further factors, which all have a direct impact for example on fibre fermentability (Beukema et al., 2020). Fermentation of the polysaccharides will be a central theme governing dietary fibre research in the future.

Understanding the role of complex fibre mixtures as substrates for the complex mixtures of intestinal microbiota is still very simplified, and the factors governing fermentation and resulting metabolites are somewhat poorly characterised. Furthermore, dynamic interactions with the intestinal mucosa and mucosal microbes, as well as the direct impact of fibre on immunological responses, are only recently established and are not yet understood in detail. Both fermentation and mucosal interactions are heavily impacted by the viscosity of fibre polysaccharides in the gut lumen – a factor which has a high variability between individuals and one that is poorly predictable by *in vitro*-methods. Finally, the chemical interactions between fibre and other small molecules and nutrients (e.g., sugars, bile acids, minerals) are still insufficiently understood, despite being acknowledged as one of the mechanisms governing nutrient absorption.

4.1.3. Required research activities

Future research in nutritional polysaccharides should aim to establish the relationship between various fibre characteristics and the resulting health effects. On a molecular level, the first step is to use advanced analytical techniques to obtain a detailed characterisation of the structural features of the polysaccharides (e.g., monosaccharide composition, substitution patterns, linkage types, see Section 3.3). Though such structural characterisation has been carried out in the past, information on the variability of such structural features within various plant sources and after their processing for food use has not been fully established. Furthermore, most of the studies on the health-promoting effects of nutritional polysaccharides have compared various fibre species (such as arabinoxylan *vs.* beta-glucan *vs.* pectin), but not different versions of a single fibre type. (e.g., relative ratios of monosaccharides involved, substitution type and degree, and type of glycosidic linkages) and how these vary in their technological functionalities or nutritional properties (especially those related to digestibility and fermentation) that rely on the specificity and access of microbial and/or exogenous enzymes to hydrolyse the fibres. Such assessment is important to be carried out with mixtures of dietary fibre and microbial cultures to create realistic conditions for complex mixtures to understand cascades of reactions, where one microbial species converts one species of fibre polysaccharides into a state that is better fermentable by the next groups of microbes.

Characterisation of fibre polysaccharides and their technological and nutritional properties should be assessed at various length scales, from oligosaccharide via soluble polysaccharides to large insoluble polysaccharides. For example, arabinoxylans (main dietary fibre component in grains such as wheat, rye, barley, and corn) but also other grain fibres are known to have significantly different properties at different scales. In the native seeds, insoluble high molecular weight arabinoxylans contribute up to 90 % of total arabinoxylan and exert a strong water-holding capacity that contributes to the technological properties of doughs, as well as bread during storage (Maina et al., 2021). Processing of the arabinoxylan through milling, extrusion, enzyme treatment, fermentation, baking, or other similar processes solubilises part of the insoluble arabinoxylans to lower molecular weight water-soluble arabinoxylans, which increase the viscosity of solutions, and build gel structures, as well as increase digestibility and fermentability. Finally, when digested to the shortest oligosaccharide level, arabinoxylans show again improved digestibility and additional functions as anti-microbial agents. Assessment of the fermentability of dietary fibre and their optimisation also links directly to the efficiency of fibre-rich materials as animal feeds, which may be optimised through fibre processing. Such overall improvement of conversion factors has an incredible effect on the sustainability of food chains through the better conversion factors and thereby improved use of existing materials, but also the optimised use of new food raw materials from protein and fibre-rich side streams from microalgae, insects, and new plant sources.

At the macromolecular level, the assessment of the fibre functionality should go beyond the currently well-established functions related to viscosity increase in the gut lumen. As any ingested food is significantly diluted by gastric fluids (several hundred millilitres depending on the individual), a pure increase in viscosity is unlikely the only mechanism governing the modulation of the absorption rate of nutrients in the gut. Recent advances in the methodologies to characterise and quantify interactions of the dietary fibre with mucosal glycoproteins or absorbable nutrients should be systematically applied to explain the interactions between different fibres and nutritionally relevant associated molecules (Padayachee, Day, Howell, & Gidley, 2017). Only with a thorough understanding of the interactions, it is possible to optimise them in foods for best health outcomes.

Finally, to maximise the nutritional benefits of fibre-rich foods and fibre ingredients, a systemic understanding of the various mechanisms of action for fibres at different conditions is needed to decide, whether for example structural features of one fibre are more important than the optimised fermentability of another fibre. The ultimate aim of the research in the upcoming years should be to make even more detailed recommendations for fibre intakes that are not based on the total dietary fibre, but at the very least based on proportions of soluble and insoluble fibres, or even better with the more ambitious goal of going for a more detailed level of fibre species and structures to fully appreciate and benefit from the enormous potential dietary fibre and the impact on our health and well-being they offer.

4.2. Food-structuring agents and in situ structurising polysaccharides

4.2.1. Current challenges

Isolated polysaccharides and complex polysaccharide assemblies, such as plant cell wall fragments, can be readily utilised to achieve a diverse spectrum of structures in foods and beverages: from viscosified fluids down to the formation of gels and complex solids, including composite coatings and films (Padayachee et al., 2017). Although polysaccharides represent a large share of the commodity and ingredient market, they are vastly underutilised within the food industry. The complexity of polysaccharide structures and the intricacy of their interactions make the task of rational material design difficult. Below, we outline four cornerstone challenges that have seen marked progress in the last decade.

The first challenge is the lack of precise control of the structuring mechanism and ability to tune underpinning interactions in order to manipulate and design targeted structures. This challenge, in part, is associated with the diversity of processing methods and structures: viscous and viscoelastic solutions, gels formed through physical and chemical cross-links, jammed semi-solids composed of concentrated suspensions, spun fibre and fibre mats, as well as liquid crystalline systems, such as cellulose colloids and nanocrystals. When polysaccharide structuring is underpinned by hydrogen bonding, charge- or dipole interactions, and van der Waals interactions, our understanding of processing-structure-function-relationship is fair. Significant gaps in understanding remain with regards to bond polarizability and establishing the precise space of polysaccharide conformations (Anggara et al., 2021; Anggara et al., 2023; Guvench et al., 2011; Watanabe, Yagi, Yanaka, Yamaguchi, & Kato, 2021). For hydrophobic and weakly hydrophilic polysaccharides, the description of entropic interactions, including the hydrophobic effect, remains elusive due to the lack of detailed experimental data and shortcomings in theoretical and modelling approaches (Benselfelt et al., 2016). Recent studies have been focusing on uncovering less explored facets of entropic interactions associated with extensive hydration of polysaccharides and the resulting interaction mechanisms rooted in the competition for water concepts (Lopez-Sanchez et al., 2022).

The second challenge is associated with a marked lack of understanding of the links between the structure of complex polysaccharides (including primary structure, functional group, side-chain motif distribution, and molecular architecture) and the resulting sets of physicochemical properties, such as surface adsorption and gel formation (Berglund et al., 2020; Yu, Stokes, & Yakubov, 2021). The need is driven by a significant increase in the use of complex polysaccharides derived from plant cell wall fragments, brans, and mucilages (Beukema et al., 2020; Yu et al., 2017). In addition, many emerging food ingredients are derived from the valorisation of waste or the upcycling of biomass. These processing methods result in the production of complex polysaccharide mixtures, the behaviour of which needs to be understood to make them useful in food structuring and as functional dietary fibre (Ren, Yakubov, Linter, MacNaughtan, & Foster, 2020; Williams, Mikkelsen, Flanagan, & Gidley, 2019).

The third challenge is associated with the need to develop efficient and sustainable processing methods for raw materials. These methods should be underpinned by quick and inexpensive assays for accurate and comprehensive structure characterisation. The recent decade saw the development of novel enzymes obtained through synthetic biology approaches, complex fermentation processes, as well as food-grade chemical and physical combination methods, such as hydrothermal, microwave, tribomechanical, ultra-sound, cold plasma, and pulsed electric field processing (Foster et al., 2020). Underpinned by progress in genetic and metabolomic analysis, biotransformation technologies, in the form of controlled germination and complex, multi-stage fermentation, have received significant development for the production of targeted polysaccharides and fibre materials (Gan et al., 2021; Reid, Yakubov, & Lawrence, 2022). Finally, the generation of food-compatible deep eutectic solvents and advances in synthetic biology elevate the attractiveness of enzymatic and solvent/chemical modification methods. Equipped with new precision processing methods, we can target the development of novel, minimally processed food ingredients (Li, Zhang, & Dhital, 2019).

The fourth challenge is associated with the sourcing of environmentally sustainable ingredients and feedstocks. A shift from engineering applications to biomedical and food puts significant pressure on the traceability and safety of ingredients, including microbiological safety. In recent years, the food industry has experienced a shortage of commodity polysaccharides, such as guar gum and gum arabic, which are produced within localized geographical areas. The key to this challenge is the ability to find alternatives and develop a diverse portfolio of ingredients to avoid monoculture-focused agricultural production that heavily relies on a streamlined economy of scale and exploitative use of the land.

4.2.2. Expected achievements and developments in the next 20 years

The next decades should see the development of precision modification and transformation processes rooted in the in-depth understanding of the structure of polysaccharides and how it translates to technical or in-gut dietary fibre functionality. Building multi-scale models of polysaccharide assemblies: from individual complex molecules and architectures to complex microstructures, will allow precise targeting of specific structural features and modification of tailored structures, as well as introducing food-compatible functional chemical groups. These advances will be further underpinned by developments in sustainable agriculture, agile bioprocessing of complex feedstocks, and the use of machine learning and artificial intelligence (AI) approaches for process development and rapid/high-throughput screening.

It is envisaged that the next generation processing of the polysaccharide ingredients will see the rise of less processed materials such as primary/secondary cell wall particles and complex cellulosic pulps with high hemicellulose content. The wider use of a diverse base of fruits, vegetables, cereals, and pseudo cereals will see broader utilisation of complex macromolecules such as xylans and rhamnogalacturonans that feature complex side-chain decorations, atypical linkages, and intricate structural motifs. Materials derived from valorised waste streams, microalgae, and marine resources will receive a boost in the ability to reduce undesired protein and phenolic contaminants that may negatively impact food safety and quality.

The next generation of processing will continue focusing on targeting improved specificity and precision of traditional applications such as food structure (thickening/rheology, water holding), storage/shelf-life stability, and fat replacement. This will be achieved by superior control over fibre microstructure and assembly, molecular weight, branching, and chemical modification (e.g., acetylation, methylation, oxidation). Continuing effort will be placed on understanding *in situ* polysaccharide modification and transformation during oral processing, digestion and colonic fermentation.

The new technologies to modify fibres will be enabled through a range of pre- and post-farm gate facilities, ranging from large biorefineries to smaller scale and agile foundries and food processing lines. It is envisaged that new advances in polysaccharide analytics, in-line sensors, and high-throughput screening will enable the adoption of machine learning and internet-of-things approaches to deliver precise, safe, and cost-effective manufacture with embedded principles of sustainability and life-cycle analysis.

4.2.3. Required research activities

Four key areas need to be addressed: (I) enzyme design, (II) combination processing methods, (III) high-throughput agile processing, and (IV) AI assisted food formulation and product design.

The current portfolio of enzymes, such as xylanases, is optimised for low side-chain substitution polysaccharides. The next generation of enzymes will target hyper-branched (complex) fibre molecules, enabling the processing of a much broader range of polysaccharide feedstocks. Conversely, reverse engineering approaches, such as the addition of sidechains or branches, will be supported by new research efforts in the field of glycosyltransferases. The discovery of enzymes will be facilitated by further insights into the germination and fermentation processes, allowing for the targeted assembly of complex plant cell wall-like structures with tuned fermentability and food-structuring capacity. Possible methods for such assemblies can draw inspiration from DNA-origami-like approaches, which are currently not feasible for polysaccharides due to a lack of precise structure control.

Combination processing methods that incorporate physical, enzymatic, and biotransformation approaches will address the challenges of effectively valorising and processing complex feedstocks. This will enable the reduction of anti-nutritional factors, minimise safety risks and allergy concerns, and achieve energy-efficient and optimised downstream processes such as dehydration, solubilisation, and extrusion.

Agile processing approaches that are more flexible and adaptable then conventional methods will further enhance the much-needed optimization in the food industry across different levels of technology readiness and production scales. When implemented at the points of primary production, such as farms and plantations, or in remote locations, such as for the extraction of marine bioresources, agile manufacturing platforms and on-demand processing facilities will significantly expand the range of feedstock materials available and enable the manufacturing of unique, yet affordable products. Minimising the time between harvest and processing plays a critical role in this process. These manufacturing platforms are envisaged to complement larger, more centralised facilities and manufacturing hubs. An integrated system of local, regional, and global manufacturing facilities will enable the rapid redirection of manufacturing resources, making processing streams of highly variable and diverse feedstocks efficient, resilient, and adaptable.

The improvement of operational efficiency and the ability to provide a quick response to food safety and quality issues are ideal areas for applying machine learning techniques and, more broadly, AI approaches. The impact of AI and machine learning spans various technology platforms, including planning, primary production, manufacturing, distribution, and social and behavioural domains. AI tools have enormous potential for enhancing communication with consumers and communities. They play a key role in augmenting consumer experiences and offer new avenues for product authentication, safety control, and monitoring. Perhaps the most remarkable area of AI application is the ability to map, segment, and contextualise consumer needs, motivations, and behaviours. Together with technological and scientific advances, this offers new strategies for influencing healthy food choices and the habitual adoption of nutritionally balanced diets.

4.3. Analytics of food polysaccharides

4.3.1. Current challenges

Typical for the analysis of complex carbohydrates in foods are the variability in the structure of the polysaccharides as well as the complex food matrix making the characterisation of carbohydrate structures challenging and complicated. In general, analysis of these essential molecules is underdeveloped, and we know more about the type and the level of micronutrients in foods (minerals, vitamins, amino acids) than on dominating contingent of carbohydrates. Another dominant group of compounds in food are proteins, having their own omics approaches to recognise routinely hundreds of proteins present in complex mixtures, while sequencing procedures facilitate the determination of the sequence of individual amino acids in distinct proteins, independently of their size. Due to the complexity of polysaccharides composed of many isomeric monosaccharide building blocks having a huge variation in glycosidic linkages and being branched and decorated with non-carbohydrates substituents, carbohydrates are much more complicated to analyse than other macromolecules (Amicucci, Nandita, & Lebrilla, 2019). Another reason adding to the complexity of (food) polysaccharides is the fact that these secondary metabolites are synthesised and modified *in planta* at the same time, resulting in manifold carbohydrate structures dependent on the genetic properties of the plant species, environmental growing-, ripening-, and storage conditions. Furthermore, food processing will add to the complexity and diversity of carbohydrate structures present. The last complicating factor is the fact that a selected oligo- or polysaccharide as present in food may originate from the raw material used (cereal, fruit, vegetable) but might be added as a functional food ingredient as well, the latter possibly being modified/functionalised by the ingredient producer.

The above-mentioned variety and complexity of food carbohydrates have resulted in many different approaches and techniques, all dedicated to a selected (class of) oligo- or polysaccharide(s), dedicated/specialised isolation and fractionation method or specialised analytical technique.

Among the best-characterised food carbohydrates are easily accessible oligosaccharides and individual polysaccharides as present as a food ingredient or dietary supplement. In addition, also human milk oligosaccharides are studied in quite some detail, recognising >200 different structures (Logtenberg et al., 2020). Human milk oligosaccharides and other prebiotic oligosaccharides like fructose oligosaccharides, inulin, isomalto-oligosaccharides, xylooligosaccharides, and galactooligosaccharides have been studied using infrared spectroscopy and a variety of MS techniques with a variety of analysers and dissociation techniques, e.g.; matrix-assisted laser desorption/ionization - time of flight (Maldi-TOF-) MS, tandem MS (MS^2), electrospray iontrap MS^n, and quadrupole TOF-MS, ionmobility (IM) MS (Hong, Yin, Nie, & Xie, 2021; Logtenberg et al., 2020; Ollivier et al., 2021; Wang, Zhao, Nie, Xie, & Li, 2021). These MS techniques are often preceded by powerful separation techniques like capillary electrophoresis, hydrophilic interaction liquid chromatography, porous graphitised carbon and high-performance anion exchange chromatography and reversed phase high pressure liquid chromatography (HPLC). The latter is especially used after derivatisation (labelling of reducing end, permethylation of free hydroxy groups, protection of sialic acid) of the oligosaccharide enabling a higher resolution, higher detector sensitivity or improved MS ionization of the targeted oligosaccharides. The presence of multiple isomers in a mixture (same mass, different linkage type or sequence of sugar residues) can be recognised by chromatography and by the rapid developing technique of (cyclic) IM-MS allowing a powerful gas-phase separation in the MS of isomeric oligosaccharides ranging from dimers to till degrees of polymerisation >10 during their travelling through an electric field. MS fragmentation pathways of carbohydrates have been recognised and documented in well-organised nomenclature and growing databases, but unfortunately, MS fragmentation routes strongly depend on oligosaccharides' structure, including sugar (linkage) type, anomeric position, and branching. An unambiguous identification of an individual, highly complex oligosaccharide may also involve laborious separation procedures followed by various 1D and 2D proton and carbon NMR spectroscopy techniques (Duus, Gotfredsen, & Bock, 2000). Combining of LC, MS, and NMR techniques have resulted in the recognition of >200 different human milk oligosaccharides, >100 different galactooligosaccharide structures, and numerous structures in other prebiotic mixtures, which are too often underestimated in functionality assays regarding their complexity.

A first challenge and often a pitfall in the analysis of complex carbohydrates is the determination of all sugars present. Many different hydrolysis conditions are being used, balancing between full hydrolysis of cellulosic fibres, pectins, and other rather robust polymers and conditions not damaging any fewer stable sugars like arabinose and sialic acid (Kamerling & Gerwig, 2007). A second challenge is to learn more about polysaccharides' structure in order to link this info to the specific technological or biofunctional characteristics of such polysaccharides. During the isolation of the polysaccharide from the plant/food matrix, attention should be paid to remove as much as possible of other (interconnected) food compounds like proteins, lipids, and starch, which could complicate carbohydrate analysis, without changing the structure of targeted polysaccharides.

Insoluble polysaccharides are usually solubilised by specific extractants like buffers, chelating agents, weak and strong alkaline solutions, or dimethyl sulfoxide. However, seldom will only one specific polysaccharide class be obtained. Therefore, obtained extracts are often further fractionated based on branching, size, and charge using gradual ethanol precipitation and by (semi)preparative size exclusion chromatography and ion-exchange chromatography. Physical characteristics of food polysaccharides in models and in food systems can be monitored by a wide range of quite diverse techniques ranging from microscopy (confocal laser scanning microscopy, electron microscopy, atomic force microscopy) to shear force-, viscosity-, and texture analysers.

4.3.2. Expected achievements and developments in the next 20 years

To be able to monitor the fate, structure, and modification of food polysaccharides in the plant, in food processing, and during digestion/fermentation after consumption, new methods should become available to analyse complex carbohydrate samples quickly but still accurately within hours instead of days, weeks, or even months. Highly advanced imaging techniques of intact tissues and food products based on microscopy, NMR, and MS (MALDI TOF MS, reflection and transmission geometry laser ablation electrospray ionization MS and nano-desorption electrospray ionization - orbitrap or cyclic-IM-MS) will be further developed and become available for the food industry to monitor reactions, accumulation of reaction products, and disappearance of other compounds at certain spots within the food product. Capsules now readily available for drug delivery at specific locations in the intestinal tract of patients will be converted to remote sampling devices, able to sample non-invasively lumen content to be analysed for microbiota composition, remaining dietary fibre, short chain fatty acids, and glycosidic degradation products like oligosaccharides, which will help us to consider personalised nutrition and to understand much better the role of dietary fibre and prebiotics for a healthy gut.

Dedicated methods to specifically extract special polysaccharides from inaccessible and insoluble matrices using planetary ball milling, ionic liquids, and specific food-compatible deep eutectic solvents will provide new insights in how polysaccharides are involved in the interaction and interactive network within food products. These insights will lead to approaches to use the entire crop in food products by tailoring the polysaccharides *in situ* by dedicated enzymes and by novel food processes like high-pressure processes, special shear forces, and ultrasound technologies. Functionalising fruits, vegetables, and cereals' own polysaccharides will also lower the ongoing need to add functional polysaccharide ingredients to tailor food simply by making use of the products' own polysaccharide portfolio.

The characterisation of polysaccharides by sequencing the polysaccharides' sugar chain through chemical and enzymatic fingerprinting and subjecting the diagnostic oligosaccharides released to LC-MS identification and quantification will lead to an adequate understanding but also to improved functionality of polysaccharide ingredients (Jermendi, Beukema, van den Berg, de Vos, & Schols, 2022). This sequence-based information will allow the distinction between polysaccharides having the same chemical characteristics but different substitution pattern, i.e., distribution of substituents over the polysaccharides' backbone. Examples are already available to illustrate that differences in substitution patterns are causing huge variance in gelling, and viscosifying properties, in fermentability and in immune stimulation.

4.3.3. Required research activities

The key to establish structure-function-relationships of food polysaccharides is to run functionality assays with well-characterised polysaccharides instead of poorly described averaged recipes and diets. Know what you investigate! This is not easy to achieve when working with mixtures of different structural molecules, all belonging to the same polymer class. This challenge becomes even larger when dealing with the insoluble and inaccessible food matrix. Accurate visualisation and characterisation procedures should be further developed and improved, but even more importantly, they should gain factors in analytical run time and should even become high throughput. Manual fractionation protocols should be automated, and different forms of chromatography could be combined in the 2D-LC-MS-MS-MS approach. For such, enzymatic and chemical methods to on-line, in between analytical columns, yield diagnostic oligomers within a range of degrees of polymerisation from 2 to 20 should be developed without losing labile substituents like arabinose, acetyl- and feruloyl groups, and methyl esters. Methods available in research should be transferred to a more routine environment while still delivering as many details as possible. Big data approaches should assist in controlling the almost unlimited flow of MS and MS^n spectra from automated extraction-2D-LC-reaction-LC-MS^n to identify individual oligosaccharides, and accurate and adequate databases should be built.

5. Polysaccharides in biomedical and well-being applications

The inherent biological and pharmacological activities, biocompatibility, biodegradability, distinctive physical and chemical properties of polysaccharides, and the versatility of their derivatives have been extensively exploited to create biomaterials and medicinal products applied to clinical practice, under clinical trials, or in *in vivo* experiments. The scientific and biotechnological interest devoted to polysaccharides in biomedicine conflates five principal research topics: 1) Bioactive Polysaccharides, 2) Cosmetics, 3) Drug Delivery and Nanomedicine, 4) Medical Devices, and 5) Tissue Engineering and Regenerative Medicine. Such a platform can lead to the development of products with a lower carbon footprint at the end of the product cycle and a valuable alternative to polymers derived from fossil sources. Some considerations for innovative clinical applications and translation, processability, performance improvement, market introduction, and future perspectives of next-generation polysaccharide biomaterials are highlighted below:

- selective chemical and enzymatic functionalisation strategies of polysaccharides using sustainable approaches
- processes for extraction and purification of polysaccharides involving green chemistry
- accurate, rapid, and high-throughput methods for multiparametric analyses of chemical and physical properties of formulations
- pharmacokinetic studies to determine absorption, distribution, metabolism, and excretion of polysaccharide derivatives
- modelling and simulation methods for the investigation of structure-performance-relationship investigation
- personalised pharmaceutical dosage forms and improvement of drug activity and bioavailability
- development of new targeting agents and smart carriers for drugs
- medical devices with anti-inflammatory, anti-infective, and anti-coagulant activities
- use of polysaccharides to produce protective medical equipment
- design and (bio-)fabrication technologies of biomimetic and functional multiscale constructs, combined with cells or bioactive factors, with highly controlled properties

- expansion of emerging therapeutic applications on *in vitro* disease modelling and microtissue formation and maturation
- additional and wide clinical trials and harmonised regulatory frameworks

The toolbox of polysaccharides available and their inherent characteristics establish a comprehensive range of opportunities for the synergistic development of innovative systems. We expect that these examples may outline forthcoming directions in biomedicine and biotechnology, which will expedite the clinical use of natural polysaccharide materials and prospect manufacturing and analysis processes.

5.1. Bioactive polysaccharides

5.1.1. Current challenges

Polysaccharides have been ingredients in traditional medicines since antiquity. This includes remedies prepared as water extracts from plants and other organisms that have proven helpful for treating various ailments. However, the role of the bioactive polysaccharide components and how they could contribute to healing was not understood. The polysaccharides in such traditional medicines are mainly obtained from plants, animals, or fungi, whereas polysaccharides in modern medications can also be sourced from microorganisms. Currently, polysaccharides are incorporated as the bioactive component in drugs, nutraceuticals, cosmetics, and other products. The function of these polysaccharides includes anti-coagulant, anti-microbial, anti-viral, antioxidant, cholesterol-lowering, anti-lipidemic, haemostatic, and adjuvant activity as well as tumour suppression, regenerative and rejuvenating action, and immunomodulation. The biological action is mostly mediated by the binding to cell surface receptors, different types of cytokines, and plasma proteins, but polysaccharides also interact with other molecules such as lipids or radicals. The biological activity is either based on the mammalian origin (e.g., heparin) or, when obtained from other species, often modulated and further enhanced by chemical modification and conjugation to introduce receptor targeting moieties, specific binding domains to proteins with regulatory functions (e.g., cytokines), drugs, and other biomolecules. Polysaccharides and polysaccharide conjugates in general possess low toxicity and are compatible with living tissue under many circumstances due to their native structure, which is a significant advantage when considering clinical applications. Biodegradability and predictable metabolic fate also reduce the probability of unexpected adverse reactions. Furthermore, chemical derivatives with modified structures are now also important. An example of modern medicines developed from traditional remedies is Krestin, a β-glucan polysaccharide extract from the mushroom *Trametes* (*Coriolus*) *versicolor*. It is a T-cell proliferation stimulator approved as a prescription drug for cancer therapy in Japan in 1977 and is currently used as adjuvant therapy for cancer.

Another important example is heparin, an anionic sulfated glycosaminoglycan discovered as an anti-coagulant in the 20th century. It is isolated from porcine and bovine internal organs and has been widely used since the 1930s. It binds to anti-thrombin III and induces a conformation change increasing greatly its affinity to active blood coagulation factors, particularly factor Xa and thrombin. Heparin is used to prevent thrombotic events and is included in the World Health Organization list of essential medicines (WHO, 2023). In general, the polysaccharide sequence regarding (i) types of monosaccharide units, (ii) pattern of glycosidic linkages, and (iii) the regioselective functionalization with sulfate and carboxylic groups plays an important role for the functional activity of glycosaminoglycans like chondroitin sulfate, dermatan sulfate, heparane sulfate, and heparin (Köwitsch, Zhou, & Groth, 2018). Analysing these sequences and their unique biological structure-property-relationships poses major challenges to polysaccharide analytics and chemistry. As an example, the therapeutic action of heparin is related to a pentasaccharide sequence that is characterised by a specific sulfation pattern with presence of *O*-sulfonates and carboxylates with a repetitive sequence of 2-*O*-sulfated iduronic acid linked to a 6-*O*-sulfated glucosamine (Mohamed & Coombe, 2017). It has also been found that 3-*O*-sulfation of glucosamine is essential for the anti-Xa activity of the pentasaccharide (Nahain, Ignjatovic, Monagle, Tsanaktsidis, & Ferro, 2018).

Unfractionated heparin is associated with serious side effects such as bleeding, thrombocytopenia, and others, which is also related to the binding of unfractionated heparin to many other plasma proteins. In addition, it has a very short half-life of less than 1 h. Nowadays, depolymerised low molecular weight versions are preferred, and different synthetic and chemically modified oligosaccharides like Fondaparinux and Idraparinux have also been introduced as heparin analogues. Fondaparinux represents a pentasaccharide, which is a methylglycoside analogue of the natural anti-thrombin III binding pentasaccharide sequence. The methylation reduces the non-specific binding to other plasma proteins. It has longer half-life than low molecular weight heparins and does not induce thrombopenia. Idraparinux is a hypermethylated derivative of Fondaparinux with an extended half-life. Whereas daily administrations are required for fondaparinux, a weekly subcutaneous administration of Idraparinux is sufficient to maintain a therapeutic effect. A disadvantage of these heparin analogues is that protamine cannot be used to neutralize their anti-coagulant activity like in the case of heparin. Hence, Idrabiotaparinux as a biotinylated derivative of Idraparinux represents a safer drug since avidin can be administered as an antidote when bleeding complications occur.

Chitosan (poly-β-1-4 D-glucosamine) is a cationic polymer that has an anti-microbial effect and can be used to induce coagulation. These properties have been utilised in dressing, such as HemCon®, to stop bleedings and for wound treatment. Chitosan can also stimulate tissue regeneration and has been used in bone cement and tissue engineering scaffolds. Moreover, chitosan and its derivatives have been used to promote tight junction opening in drug delivery applications and as an adjuvant for vaccines.

Acarbose is a tetrameric pseudo-oligosaccharide that inhibits intestinal alpha-glucosidase. It is an anti-diabetic drug used to reduce glucose uptake and lower blood glucose levels. Sugammadex is a γ-cyclodextrin (cyclooctaamylose) derivative introduced as a drug to reverse the effect of the steroidal neuromuscular blockers rocuronium and vecuronium, which are medications used as muscle relaxants in major surgery. Sugammadex forms a 1:1 inclusion complex with these neuromuscular blockers and is used in an emergency to reverse life-threatening respiratory suppression and aid recovery following surgery. Other cyclodextrin derivatives, such as hydroxypropyl β-cyclodextrin and sulfobutyl β-cyclodextrin, have also been introduced as complexing excipients used to stabilise, solubilise, and aid the dissolution of lipophilic drugs. These cyclodextrin derivatives have been included in drug formulations approved for oral, ocular, intramuscular, and intravenous applications.

Notwithstanding the long history of polysaccharide use in medicine and the recent introduction of synthetic and semi-synthetic oligosaccharide drugs, there are considerable challenges that need to be overcome to reach the true therapeutic potential for this class of molecules. Advances in our understanding of their role in inter- and intracellular communication, interaction with other biomolecules, and receptor binding are needed. This especially applies to their role in modulating immune responses. Improved knowledge could contribute to the development of therapeutic polysaccharides, including new vaccines and treatments for autoimmune diseases and cancer investigations to determine the structure-activity-relationship is a vital part of the discovery and development of synthetic and semi-synthetic drugs. Such studies are very challenging for complex polysaccharide conjugates and derivatives. Natural polysaccharides are a mixture of structural isomers with different molecular weights, side-chain distribution, and structure. Chemical modification leads to further increased structural variation between individual polymer chains. Chemical analysis can be very challenging to fully characterise and define all aspects of this structural complexity. This is also a significant issue for manufacturing under *Good Manufacturing Practice* and standardisation of polysaccharides as therapeutic substances. Efficient delivery is also an issue. Polysaccharides are hydrophilic macromolecules that cannot be absorbed intact from the gastrointestinal tract or through the skin. Thus, systemic administration or the utilisation of advanced delivery systems, such as nanoparticles and liposomes, may be needed to reach drug targets in the body.

5.1.2. Expected achievements and developments in the next 20 years

Modified polysaccharides such as hydroxypropyl methyl cellulose, methyl cellulose, and carboxymethyl cellulose are widely used as excipients in oral and topical drugs as fillers, dissolution enhancers, thickeners, and coating materials. Hydroxypropyl methyl cellulose is also used for therapeutic action in artificial tear formulation. These derivatives are generally considered safe and lack toxicity also in subcutaneous and intravenous administration. Additionally, they are widely used in cosmetics, including skincare and haircare products. Thus, it is well established that polysaccharide derivatives can be safely used in medicine.

Polysaccharides are generally recognised as safe for human use. Many polysaccharides are hydrolysed by enzymatic action to form mono- or oligosaccharides identical to endogenous carbohydrates in the body. Therefore, the formation of toxic metabolites, which need to be considered for other non-biological drugs, is unlikely. Chemically modified polysaccharides are, in general, not absorbed after oral intake and will be excreted intact in faeces. Parenterally administered oligosaccharides, polysaccharides, and their derivatives are thought to be eliminated mainly by renal secretion.

Investigations to explore the therapeutic potential of natural polysaccharides will continue. These will especially focus on immunomodulatory substances for treating cancer, inflammation, and other diseases. The use of polysaccharides and polysaccharide-based material to stimulate tissue regeneration is a strong focus in biomaterial research and cosmetics. In this context, the clearance of polysaccharides from the human body must be discussed. Some polysaccharides like chitosan, dextran, and amylose are degraded enzymatically within the human body. Others like cellulose are more stable due to the lack of the corresponding degrading enzymes (e.g., cellulases) and have to either remain within the body or are cleared by other mechanisms such as oxidative degradation.

The development of biologically active chemically modified carbohydrates is only starting, with a few approved drugs in current use. Further advances in carbohydrate chemistry will allow more efficient synthesis and selective modification. Detailed structure characterisation will help to realise the full potential of synthetic and chemically modified oligo- and polysaccharides as active pharmaceutical ingredients.

Nanoparticles based on polysaccharides are promising for therapeutic application. The inherent biocompatibility and biodegradability of polysaccharides such as chitosan, hyaluronate, and alginate can thus be exploited to improve the delivery of drugs. In addition to serving as the core material for the polymeric matrix of the particles, these biopolymers can be chemically modified to introduce receptor ligands to target specific cell types.

5.1.3. Required research activities

Studies *in vitro* and *in vivo* are necessary to better understand the role of polysaccharides in the communication between cells, cell adhesion, and guiding the protein binding. Further development of selective chemical and enzymatic modifications are needed to precisely tailor the structure of polysaccharide derivatives and conjugates with drugs, peptides, proteins, and other bioactive moieties. Investigations to improve the efficiency and precision of analytical techniques such as NMR and SEC-MALLS are needed. This should also include more advanced techniques such as cryo-electron microscopy and ToF secondary ion MS. Pharmacokinetic studies to determine absorption, distribution, metabolism, and excretion of modified polysaccharides. Progress in these investigations should aid detailed studies into the structure-activity-relationship and optimise the therapeutic effect. The development of improved delivery systems and efficient manufacturing technologies will also be needed.

5.2. Cosmetics

5.2.1. Current challenges

Polysaccharides, monosaccharides (special sugars) and derivatives thereof (e.g., polyols, carbohydrate-based emulsifiers and surfactants) are largely used in cosmetics as functional and active ingredients. Functional polysaccharides usually control physicochemical properties of formulations acting as gelling agents, viscosity adjusters, thickeners, emulsifiers, conditioners, film formers, and suspension agents. Different ionic (anionic, cationic, amphoteric) polysaccharides (e.g., xanthan, polyglucan derivatives, chitosan or carboxymethyl chitosan, inulin, cellulose, and starch derivatives) and non-ionic polysaccharides (e.g., starch, guar gum, and cellulose ethers) are used in this context. Active polysaccharides give skin hydrating, anti-oxidant, and anti-bacterial properties to cosmetic formulations. These include a multitude of biopolymers, such as cellulose and starch derivatives, pectin, gum, mucilage, seaweed and botanical polysaccharides as well as microbial and animal polysaccharides (Kanlayavattanakul & Lourith, 2015). Application-related properties of polysaccharides involve performance, product sensory, and product stability of cosmetics (Alves et al., 2020).

Product performance concerns the intended function of the end-product, which may, among others, cover moisturising, providing skin protection and cleansing. There exist polysaccharide-based humectants that aid in retaining moisture in films. Other polysaccharides like carboxymethyl β-glucan provide additional health benefits: the polymer assists in protecting and repairing the skin. Its revitalising effects are exploited in anti-aging products, while its protective function can be applied in sunscreen. Hyaluronic acid is a polysaccharide with nourishing and rejuvenating properties that keeps the skin supple and elastic. To support removing grease, grime, and dirt, the emulsifying and dispersant aspects of polysaccharides are highly valued. Alternatively, these polymers may support the incorporation of poorly soluble ingredients into the formulation. Methyl cellulose and carboxymethyl cellulose can be exploited for this purpose. Besides skin products, polysaccharides even play an active role in hair products. Polyquaternium-10, a polymeric quaternary ammonium salt of hydroxyethyl cellulose provides shine, radiance and mends the split ends of hair. Cationic inulin or guar can also be used as conditioners in shampoo.

Product sensory feeling describes the experience when applying the products. It covers thickness, viscosity, and smear-ability, as well as more complex sensational concepts as satiny or smooth feeling, cooling or relaxing effects, creaminess, and smoothness. Carboxymethyl cellulose, guar, and xanthan gum provide thickness to formulations, even when present in small concentrations. Hydroxyethyl cellulose assists in evenly spreading the product; it further boosts the feeling of creaminess in foams and a smooth texture to creams. Hydroxypropyl starch phosphate addition in cosmetics grants smoothness and provides the end-product with a satiny, velvety note. Sodium alginate is a well-known thickener but further applies a soothing and softening effect to the skin. Cellulose microfibres can be used as thickeners and help to suspend particles (for example, encapsulated perfumes).

Another relevant aspect is the product stability. Within product stability, different functions are covered: from binders, emulsifiers, and dispersants to surfactants. Binders provide cohesion in solid cosmetic products. Methyl cellulose and pectins both display this property. Emulsifiers aid in dispersing oil in water, while stabilisers are added to prevent unmixing of the emulsion or to prevent particle settling in suspensions. Methyl cellulose is a good stabiliser for emulsion and foams. It also coats particles preventing their agglomeration. Other frequently exploited stabilisers include hydroxyethyl cellulose and alginates.

The limited accessibility of many natural polysaccharides in large quantities and the numerous functionalisation techniques (that frequently demand the use of hazardous materials) have hampered their full potential in cosmetics. For these reasons, research expanded in three different directions to broaden the variety and availability of functional polysaccharides and materials. (I) Polysaccharide production in previously unexplored species is continuously being studied, which includes a characterisation of the properties of the biopolymers obtained by these new routes. Advancements in genetic engineering in bacteria and fungi have further widened the assortment of highly engineered polysaccharides. (II) The expansion of green chemistry principles in the context of chemical functionalisation of polysaccharides will proceed even further. The use of irritating or toxic components in the fabrication of multifunctional polysaccharide compounds will diminish in favour of greener and less toxic alternatives. Less unwanted side-products and energy consumption will be the outcome of the ever-increasing appearance of highly selective catalysts and the use of highly engineered enzymes. (III) The processing and shaping of polysaccharide-based materials in cosmetics will also see a shift towards using new technologies that are less harmful and less energy consuming.

5.2.2. Expected achievements and developments in the next 20 years

Polysaccharides have a promising future in cosmetics because of their multifunctional capabilities (abilities to combine both functional and active properties in one component, for example). Multi-functionalisation of polysaccharides can be achieved via chemical and enzymatic methods and via biotechnological routes for biofabrication of these biopolymers. Another relevant capability is the shape of polysaccharide materials such as capsules, particles, spheres, fibres, and films. The combination of multifunctionalities alongside shaping technology has a promising future to create highly engineered shapes suitable for unique product performance and sensory properties.

Future trends of polysaccharides in cosmetics involve a combination of cosmetic and pharmaceutical properties of polysaccharides, including new methods for encapsulation and stimuli-responsive delivery of active compounds and new formulation technologies for skin moisturisation and repair incorporating biological ingredients and nanotechnology. These trends target to enhance skin hydrating efficiency and protection, treat wrinkles, and provide anti-aging properties. Future business opportunities will be based on skin performance (helping with moisturisation/preventing de-moisturisation), skin sensory (the signal that you are doing something good to your skin), product sensory (the right thickness, viscosity, smear-ability of the product), product stability (including anti-bacterial activity) and opportunity for claims (e.g., attractive terms such as *naturally derived* and *nature provided ingredients*).

5.2.3. Required research activities

New technologies for sustainable production of polysaccharides, polysaccharide derivatives, and functional shapes need to be developed that include, among other things, the following aspects:

- extraction, purification, and biofabrication of polysaccharides with a focus on green chemistry principles and (bio)engineering, recycling and circularity of materials, as well as sustainable sourcing from marine and agricultural side streams
- functionalisation methods focussed on sustainable chemistry, highly engineered enzymes, solvent-free media, cell factories, and self-assembly
- design and fabrication of functional shapes with highly controlled properties (including size, shape, surface morphology, hierarchical structures, and colloidal features)
- removal of additives with potential harm to human health from the bioactive products (e.g., dysbiosis inducers and hormone-mimicking chemicals)
- fast and accurate high-throughput analytical characterisation techniques for comprehensive analyses of macromolecular properties of functional polysaccharides (preferably for multiple parameters at the same time)
- advanced methods that combine imaging and information on chemical composition (e.g., chemical microscopy)
- new methods for modelling and simulation of structure-property-relationships

5.3. Drug delivery and nanomedicine

5.3.1. Current challenges

Ever since humanity made the first attempts to fight diseases and life adverse cases, many remedies have been prepared by mixing natural components, including polysaccharides. The latter was occasionally the active components, but even more frequently, they were present as support - *excipients* - added intentionally or naturally occurring in the preparations. Over time and with the evolution of medicinal products towards more scientifically sound compositions, the role of polysaccharides evolved, and, especially in the last 150 years, polysaccharides have found rational use. In particular, the evolution of polysaccharide chemistry has allowed the creation of materials with increasingly tailored functions, aiming for the improvement of drug performances intended both for therapeutic efficacy and technological processability. It is well-known that polysaccharides and their derivatives play a decisive role in pharmaceutical formulations, carrying out multiple roles and functions. In the so-called conventional pharmaceutical preparations, biopolymers like cellulose, starch, and the various gums, to mention the most used polymer systems and their uncountable derivatives, act as fillers, aggregating or disaggregating agents, film-formers, rheological property modifiers, support materials, or adjuvants, to name the most important activities. In this sense, scientific and technological evolution has made it possible to find adequate solutions to pharmaceutical needs, working appropriately such as the characteristics of the primary structure, the molecular weight, and the backbone derivatisation with specific moieties (e.g., hydrophobic or ionisable) to confer new properties (e.g., solubility, gel-forming, rapid disaggregation, and film-forming).

Another pharmaceutical area in which polysaccharides play an important role and can find an interesting and profitable development in the coming years can be found in those systems collectively named *drug delivery systems*. These are formulations specifically designed to modulate the release of active ingredients, both in time (continuously, shot like, or modulated profiles) and in space (i.e., targeted body area such as organs, cells, and subcellular level of specific tissue) in order to maximise the effectiveness of the active pharmaceutical ingredient itself or to minimise side effects, generally associated to the specific toxic effect of conventional drug delivery. The so-called Paul Ehrlich's *magic bullet* concept is the approach underlying this pharmaceutical area, and nanomedicine adheres to this concept more closely than other delivery systems.

5.3.2. Expected achievements and developments in the next 20 years

There is no doubt that the technological level reached by now for the so-called *conventional formulations* is very high, and it can be considered mature. Moreover, the introduction of a new polysaccharide-based material, considering the complexity of the current regulations, would find its justification in a significant improvement in pharmaceutical performance. In this sense, a push forward in which polysaccharides could play a significant role replacing the fossil-based polymers currently used, or developing new formulations with advanced therapeutical or processing performances can be given taking into account their good compatibility in biological environment, beneficial physical properties (e.g., high T_g), ease of derivatisation (e.g., possibility to induce pH-responsive properties), and the abundance of the starting material, low ecological impact in production, and inertia in carrying drugs (Laffleur & Keckeis, 2020; Pooresmaeil & Namazi, 2021; Tomás, Palmeira-de-Oliveira, Simões, Martinez-de-Oliveira, & Palmeira-de-Oliveira, 2020).

A lot of drug delivery systems based on polysaccharides have been developed over the last 30 years in various therapeutic fields from the ocular to the intestinal, for inflammation, anti-microbial activity, and tumour therapy (Cui, Zhang, & Liu, 2021; Delshadi, Bahrami, McClements, Moore, & Williams, 2021; Dubashynskaya, Poshina, Raik, Urtti, & Skorik, 2020; Khatun, Toth, & Stephenson, 2020; Layek & Mandal, 2020; Mašková et al., 2020; Tomás et al., 2020). However, research to explore new opportunities in this field is not sufficiently boosted; to do this, a propulsive thrust is needed. First, new polysaccharides or oligosaccharides of different origins should be sought to exploit innovative properties, both as biocompatible and as *smart materials* with new properties, such as gelling, stimuli-responsive, mucoadhesive, cell- or organ targeting. At the same time, new chemistries capable of obtaining derivatives with smart properties should be developed.

A green and biocompatible chemistry approach could be very interesting in order to combine both problems of reducing the impact on health and safeguarding the environment. For sure, the quantities of materials involved in the creation of drug delivery systems are not comparable to the amount of polymer material involved in the production of commodities, but, inevitably, companies developing new products are very sensitive to these problems, even just for the regulations. Moreover, ecofriendly and biocompatible chemistries, as well as production processes, are more appealing from an industrial point of view. Any system to be marketed depends on the budget of the realization costs (very high in the case of non-bio and non-eco systems) and of the revenues (related to the selling price of the drug, in turn, linked to the benefits obtainable in terms of therapeutic efficacy and any reimbursement by the national healthcare systems).

Throughout this story, nanomedicine must be considered as the most promising field. At present, polysaccharides are little used when compared to their vast potential. This is mostly due to the fact that fossil-based polymers are more easily manageable in terms of tailoring. For these reasons, both the culture of polysaccharide and the promotion of the study of their properties and their use must be improved, considering that, compared to fossil-based polymers, they generally show better biocompatibility. We must go in the direction of promoting new polysaccharides that support and replace the most studied and used polymers. Hyaluronic acid, for example, is undoubtedly the first-choice polymer for its properties. Other polysaccharides can open new possibilities in terms of the realization of new nanomedicines and improved therapeutic performances. As already mentioned in the introduction of the EPNOE Research Roadmap, the next decades will require carbon footprint reduction and improved sustainability in all sectors, including pharma activities. Innovations in pharma research and industry typically take 10 years or longer to reach application in patients, and therefore offering sustainable solutions at early stages of product development is an urgent requirement. Polysaccharides have many competitive advantages to improve sustainability in pharma by replacing persistent fossil-based polymers and actives with bioactive and biodegradable alternatives.

5.3.3. Required research activities

The research in the next few years can be divided into two different development lines. For the conventional formulations, the research should be finalised to develop polysaccharide derivatives in order to improve both the production of the conventional formulation, such as tablets, capsules, solutions, suspensions, films, creams and gels, and increasing the drug bioavailability and the specificity of the formulations, tailoring interaction with the human body, including mucoadhesion, drug permeation through the biological membranes, and responsiveness to physiological conditions. In this respect, the innovation should target new polysaccharide derivatives, obtained by different routes, for:

- continuous manufacturing processes for the preparation of the pharmaceutical dosage forms
- personalised medicine in terms of new materials for new processes, such as *medicine on demand*, realised ad hoc for a specific patient
- improvement of some conventional pharmaceutical dosage forms (e.g., as parenteral, drug depot, gels, and patches)
- improvement of the drug activity (e.g., anti-microbial or stimulating immune system response)

In terms of synthesis, the innovation for polysaccharides in drug delivery systems should target:

- new biocompatible and green chemistry, thus widening the possibility to modulate the physicochemical properties in acceptable processes from the industrial point of view
- new materials for new nano- and micro-particulate platforms
- new targeting agents for organs by a recognition system based on the physiological conditions
- new targeting agents for specific receptors expressed or overexpressed on cells
- new approaches for improving the bioavailability of incorporated drugs
- new suitable materials as transfecting agents in subcellular targeting
- intelligent carrier for drugs (systems responsive to physiological conditions related to specific diseases)
- carriers that are able to modify the fate of drugs, thus renewing the life of old drugs (e.g., enhancing the activity of anti-microbial drugs to fight the new emergency in anti-biotic resistance)
- theranostic applications

It is reasonable to approach the above-depicted program with a double-step comprehensive strategy. The first topics should be studied and developed in the first phase, as they need more fundamental research, whereas the other points can be approached soon after, once the basic science reaches significant results, allowing the researchers to target specific goals by using new efficient tools.

5.4. Biomedical devices

5.4.1. Current challenges

Biomedical devices comprise extracorporeal artificial organs, such as cardio-pulmonary bypasses and artificial lungs (extracorporeal membrane oxygenation) as well as devices used in haemodialysis and apheresis (for detoxification of blood). An integral part are the blood vessel endothelia that connect the vascular system of the patients with the artificial organs or special vascular access like an arterio-venous shunt. Implantable medical devices that support and replace organ functions comprise artificial heart valves, ventricular assist devices, cardiac pacemakers, stents, and artificial blood vessels. Furthermore, all kinds of intravenous and other catheters that are either in contact with blood or other tissues (e.g., urinary catheters) are more examples. On the other hand, there is a wide scale of hard and soft tissue implants that may be used temporarily to support the healing of tissues or to permanently re-establish or replace bone, joints, breast, and other soft tissue implants for medical and cosmetic reasons, but also materials for topical and other applications like sutures, wound dressings, periodontal membranes, tissue adhesives, haemostatic agents, and sensors. Finally, disposal materials, including syringes, packaging materials, medical gloves and masks as well as other protective equipment for patients and medical staff represent a significant part of biomedical devices (Bronzino & Peterson, 2015).

It must be underlined that polymeric materials play the most important role in the area of biomedical devices. A recent industrial review on the use of polymers states that the market for medical polymer products include medical fibres and resins (about 40 %), medical elastomers (about 15 %) and biodegradable medical plastics (Grand View

Research, 2021). Fibres and resins include synthetic polyvinyl chloride, polypropylene, polyethylene, polystyrene, and other thermoplastics. However, biodegradable polymers that are mostly represented by polyesters used as suture materials take only a very small share of the global medical polymers market, which is smaller than 5 %. The number of products that are using polysaccharides-based materials is rather limited regarding the kind of biomedical devices but also the quantities used. Considering the problem that most synthetic polymers are non-degradable and represent a potential threat to our environment, it will be highly desirable to increase the share of polymers, including polysaccharides, that are degradable and feature a tailored durability within their target application.

It is predicted that the global medical polymers market will reach a value of USD 27.75 billion by the end of 2028, which is due to the growing demand for medical and pharmaceutical packaging materials, especially flexible packaging for medicines, blood bags, surgical gloves, and medical drapes. In addition, the increasing application of medical polymers in hip and joint replacement as well as spinal and cranial implants will have a significant impact on the market growth (Grand View Research, 2021). The growing market for the application of polymers also highlights the need to look for further applications of polysaccharides in the field of medical devices to reduce the consumption of synthetic fossil-based polymers with their negative impact on our environment.

Cellulose was one of the first polysaccharides used as a membrane in blood purification. First commercial devices during clinical establishment were based on cellulose, which had problems related to biocompatibility, e.g., complement activation, leading to the development of modified cellulose like cellulose triacetate and a dominance of dialyser based on synthetic polymers, e.g., polysulfones (Togo, Yamamoto, Imai, Akiyama, & Yamashita, 2018). Haemostatic materials like films and powders are required during surgical procedures or after injuries to stop bleeding. Additionally, oxidised cellulose, chitosan, and starch are used in commercial products due to their properties in activating blood platelets and coagulation processes (Chen et al., 2020). Another medical problem that shall be tackled using polysaccharides is the prevention of postoperative adhesions that can occur after surgical interventions, for example, in the visceral surgery, avoiding adhesion of peritoneum or connective tissue to the gut (Moris et al., 2017). Here, the hydrophilic properties of polysaccharides are desired to avoid the attachment of cells. For example, starch powder (microparticles) or membranes made of a combination of hyaluronan and carboxymethyl chitosan have been found to be useful (Li et al., 2008).

Heparin is not only used for anti-coagulation of blood by intramuscular injection in patients. It is also used in anti-coagulant coatings of different biomedical devices, like components of extracorporeal circulation devices, blood pumps like ventricular assist devices, vascular grafts, and stents to avoid clot formation on the surface of the devices. This also reduces the need for the prescription of systemic anti-coagulation to patients with possible undesired side effects (Biran & Pond, 2017). Moreover, an insufficiently addressed medical problem is the replacement of the vitreous body of the eye. Here, the first products based on hyaluronan (a major component of the vitreous humour) are making some progress (Li et al., 2008). Hyaluronan is also used to develop membranes that can be applied to support the repair of tympanic membranes (Martini, Morra, Aimoni, & Radice, 2000).

Overall, polysaccharides, depending on their source and chemistry, have a very broad spectrum of bioactivity that is interesting for tackling different medical problems, as highlighted above. On the other hand, processing of polysaccharides into the desired shapes like fibres, films and membranes is still challenging and may require different physical and chemical processes. Some polysaccharides like cellulose and chitin have very poor solubility and require partly harsh conditions to process them. The oldest textile technology using cellulose, the viscose process, goes back to 1925, which can be used to produce fibres, but also films and other shapes (Shearer, 1925). However, this requires the application of harsh conditions, including treatment of wood pulp using sodium hydroxide forming alkali cellulose, followed then by mixing with carbon disulfide to form cellulose xanthate, which is spun into a coagulation bath containing sulfuric acid and salts. During this process, the cellulose xanthate is transformed back into cellulose (Cook, 1984). However, this process is not environmentally friendly and has a high-water consumption too (Bredereck & Hermanutz, 2005). Now, ionic liquids also allow the extrusion of cellulose fibres, which makes the process of fibre spinning easier and more environmentally friendly (Vocht et al., 2021). However, most polysaccharides are water-soluble (e.g., alginate, hyaluronan) and require physical or chemical shaping processes, like electrospinning, freeze-drying, and chemical cross-linking, to engineer them into the desired form (e.g., fibres, films, membranes, and hydrogels).

5.4.2. *Expected achievements and developments in the next 20 years*

Properties of polysaccharides that make them interesting for future application in biomedical devices are not only related to their abundance and low price of raw materials but also their hydrophilic nature that enables them to bind water, which can reduce undesired adsorption of proteins and other body components like blood cells. Other important factors are the presence of functional groups for chemical modifications, and the inherent bioactivity of certain polysaccharides. Particularly, the latter is one of the most interesting aspects to increase their application in the field of biomedical devices. Polysaccharides, especially sulphated ones, have the potential to inhibit coagulation of blood. Heparin, as representative of glycosaminoglycans, has been known for a long time as a polysaccharide with anti-coagulant properties due to its binding to anti-thrombin III and inhibition of activated coagulation factors like thrombin (Mueller & Scheidt, 1994; Wieringa, Søndergaard, & Ash, 2021). However, cellulose sulfates and other sulfated polysaccharides have been shown to inhibit the coagulation system and could replace heparin in several applications (Groth & Wagenknecht, 2001; Mestechkina & Shcherbukhin, 2010). Also, material combinations made of chitosan and pectin demonstrated excellent blood compatibility when used for making vascular patches (Bombaldi de Souza et al., 2019).

Polysaccharides also have an adsorptive capacity to remove uremic and other toxins, immune globulins, cytokines that play a role in end-stage renal diseases, autoimmune diseases, leukemia, sepsis, and others. Removal of uremic toxins by adsorption on lignin-binder or polysaccharides from algae are some reported examples (Sandeman et al., 2017). Moreover, the removal of proteins like low-density lipoprotein from the blood of patients in hyperlipidemia by heparin-mediated extracorporeal low-density lipoprotein precipitation apheresis using heparin has been reported as well as the use of particles made of dextran sulfate immobilized onto cellulose for binding of cytokines such as tumour necrosis factor that plays a role in sepsis on particles made of activated cellulose (Jaeger, 2003; Weber et al., 2005). However, the full potential of polysaccharides for biomedical applications has not yet been reached, which requires investments in research and development of new products.

5.4.3. *Required research activities*

Heparin is an efficient anti-coagulant but must be isolated from animal sources, particularly the mucosa of the small intestine of pigs. This is a time-consuming process resulting in high variability of activity and risks of contaminations that can represent a threat to patients (Liu, Zhang, & Linhardt, 2009). Therefore, for clinical application as systemic anti-coagulant, synthetic heparins might become dominating if the prices were lower than that of natural products. Attempts to establish a solid-phase synthesis of synthetic heparins have been undertaken by Seeberger et al. and chemoenzymatic synthesis of heparins has been reviewed recently (Seeberger & Werz, 2005; Wang, Liu, & Voglmeir, 2020). First synthetic heparins (pentasaccharide) with anti-Factor Xa activity preventing deep vein thrombosis are already on the market (Zhang, Zhang, Tan, Pan, & Zhang, 2019). It is expected that the use of synthetic or semisynthetic heparin analogues will increase during the next decade.

Anti-coagulant surface coatings of medical devices like extracorporeal devices, blood pumps, blood linings, catheters and cardiovascular stents that are currently based on heparin could benefit from the use of other polysaccharides that possess anti-coagulant effects (Martini et al., 2000). A reason for such replacement of heparin can be its relatively high cost and the lack of long-term stability regarding its anti-coagulant activity. Herein, the discussed anti-coagulant activity of different sulfated polysaccharides, like cellulose sulfates, has not been explored to a sufficient extent regarding anti-coagulant effects, the durability of coatings, and potential risks and side effects (Bombaldi de Souza et al., 2019; Sandeman et al., 2017). It is anticipated that anti-coagulant coatings for biomedical devices by semisynthetic heparin analogous polysaccharides will increase during the next decades.

Representatives of polysaccharides possess anti-inflammatory properties, which are known to be related to their ability to bind pro-inflammatory cytokines, to block binding of leukocytes to endothelial and other cells by inhibiting selectin-related cell-cell adhesion and to block pro-inflammatory signal transduction in monocytes/macrophages and other white blood cells (Köwitsch et al., 2018). Recent studies have also shown that coating material surfaces with glycosaminoglycans such as heparin and hyaluronan could be used to provide surfaces with anti-inflammatory properties that reduce activation of macrophages as a key player of innate immunity (Alkhoury et al., 2020; Zhou, Niepel, Saretia, & Groth, 2016). Also, different polysaccharides from plants possess anti-inflammatory effects, as recently reviewed, which may open new avenues for application (Hou, Chen, Yang, & Ji, 2020). Several polysaccharides possess anti-infective properties against bacteria, viruses, and fungi (Xie et al., 2016). Chitosan is a well-known example in this context, however, this area should be further developed (Abd El-Hack et al., 2020).

A further example of advanced research activities required for the use polysaccharides is their application as components of protective face masks to replace polypropylene that is dominating the materials for making fibres as major component of masks (O'Dowd et al., 2020). Chitosan or cationic chitosan derivatives have emerged as new materials for the production of fibres that can bind and destroy bacteria and viruses by electrostatic interaction (Abbas et al., 2021; Choi et al., 2021).

5.5. *Tissue engineering and regenerative medicine*

5.5.1. *Current challenges*

Multiscale constructs composed of polysaccharides combined with cells or bioactive factors have been extensively and successfully explored in preclinical studies as exogenous extracellular matrices for bone, cartilage, skin and cardiac tissue regeneration or integration. Nonetheless, only a small number of products employing a restricted number of polysaccharides, including alginate, hyaluronic acid, chitosan, and chondroitin sulfate, have reached the clinical realm, bearing in mind that quality, safety, efficacy, useability, and cost are hallmarks for their introduction in the market.[4]

Polysaccharide-based tissue engineering constructs may carry some of the risks associated with pharmaceuticals and medical devices but are likely to exhibit greater variability in composition, structural reproducibility, and performance since the structure of the biopolymers differs from in terms of the source, purification process, batch, and molecular weight. The complexity of the biological interface and immunogenicity, and the inadequate establishment of polysaccharide structure-property-function-relationships (both physical and biological) owing to chemical group modification can also pose regulatory and therapeutic translational challenges.

5.5.2. *Expected achievements and developments in the next 20 years*

The functional and structural diversity of polysaccharides prone to be processed into diverse architectures, conjointly with the abundance and renewable character of their sources (e.g., algae, plants, and microorganisms) will continue to fuel polysaccharide-based applications in tissue engineering owing to their specific chemical versatility, biodegradability, and biocompatibility (Azevedo, Mano, & Borges, 2021; Zhu et al., 2019). Such a concept can lead to the development of user-programmable biomaterials with a lower carbon footprint at the end of the product cycle and a valuable alternative to polymers derived from fossil sources.

The toolbox of polysaccharides available and their inherent characteristics can establish a comprehensive range of opportunities for synergistic fabrication through 3D/4D bioprinting and electrospraying technologies of innovative multifunctional hybrid systems (e.g., bioinks, cell-laden adaptable hydrogels, bioactive composites, films, or injectable capsules loaded with extracellular vesicles) with improved performance and spatiotemporally controlled design. In this sense, investigating cell-material interactions are noteworthy to promote the integration of biological, physicochemical, mechanical, and topographical cues into biomaterials in order to recapitulate tissue-scale organization, the pallet of dynamic features of human tissues, and vascularisation within the implant (when necessary).

5.5.3. *Required research activities*

Rational design of biomaterials at the molecular, macromolecular, and topological levels with tailored stimuli-responsive properties for controlled interactions with cells will be required to advance the field, as well as smart materials suitable for advanced processing while maintaining desired mechanical, physicochemical, and biological properties.

The development of new and simple advanced therapy medicinal products, systematic studies, and additional clinical trials urge us to try to find meaningful answers. Therefore, larger sample sizes, randomised control groups and long-term follow-up reports are important to empower such clinical studies and investigate rare adverse events. Rational and precise tissue engineering products and processes are evolving, although clinical translation and commercialisation are time-consuming and not always feasible. Hence, the debate should necessarily contemplate the manufacture, quality standards, and scale-up of implantable scaffolds from the research and development standpoint, their practicality, off-the-shelf use, cost-effectiveness, and business model, but also the preparation of harmonised wide regulatory frameworks to accelerate their introduction into the clinical practice in collaboration among academics, clinicians, companies, and regulatory authorities.

6. Polysaccharide Chemistry, Biology & Physics

In the next 20 years, a demand with high societal and political priority is the replacement of fossil-based products and synthetic polymers thereof in our daily life needs. In line with sustainability, protection of resources, and most importantly, care for the environment in all aspects, polysaccharides from renewable resources are most suited to fulfil this role. Novel techniques and methods in chemistry, biology, and physics will provide novel and innovative polysaccharide-based materials with defined properties on the molecular level that are specifically tailored for emerging applications. The challenges, necessary actions, and opportunities in these three major areas are manifold.

In Chemistry:

- transition of novel efficient synthesis approaches from academia into commercial products and large-scale production
- exploration of sophisticated organic synthesis concepts and homogeneous reaction media

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[4] https://clinicaltrials.gov.

- utilisation of novel types of polysaccharides, e.g., from marine sources, biotechnological processes, and waste material valorisation, as starting material for chemical synthesis
- adaptation of highly efficient and selective chemical and chemo-enzymatical synthesis into polysaccharide research
- development of methods for the fabrication of novel types of semi-synthetic polysaccharide derivatives and well-defined all-polysaccharide-*co*-polymers for advanced applications
- efficient control over the monosaccharide sequence and chemical functionalities therein

In Biology:

- new efficient methods for fine-structure determination of polysaccharides on the molecular level and understanding of their relation to functional properties *in vivo*
- production of polysaccharide structures with defined molecular structure (in particular regarding the degree of polymerisation, polymer backbone, and branching pattern) using novel chemo-enzymatic procedures harnessing a combination of *in vivo* and *in vitro* synthetic biology
- elucidation of polysaccharide biosynthetic pathways using multidisciplinary approaches
- development of methods for the *in situ* analysis of intact biological assemblies at a nanometer scale
- better understanding of the role of specific monosaccharide sequences of polysaccharides in biological systems and how they are controlled during biosynthesis

In Physics:

- development of fundamental research to tune the chain dynamics and interactions of polymer chains in polysaccharides
- understanding the physical properties *vs.* the structural perfection/imperfection
- machine learning and AI for finding solutions based on new approaches and agreed protocols constructed in large data libraries
- development of multiscale simulations and models to design functionalities and properties of polysaccharides

The concerted research activities will be triggered by the identification of the needs of society and the environment. Targets and demands will be identified and tailored polysaccharide-based materials fabricated by the developed methods and techniques fulfilling the requirements will be applied.

6.1. Chemistry

6.1.1. Current challenges

A beneficial societal factor of polysaccharide research is the increasing public awareness of the need to replace fossil-based products with more sustainable alternatives coupled with an increasing acceptance of the higher costs usually associated with biobased products. Polysaccharide chemistry faces several challenges, which are quite different from medium-sized carbohydrate structures as well as conventional organic and polymer chemistry. Therefore, organic synthesis methods from low molecular carbohydrate structures cannot simply be transferred to polysaccharides. Chemical modification and characterisation of polysaccharide materials and modified polysaccharides are still big challenges. Only a humble selection of the highly efficient synthesis methods known in modern organic and polymer chemistry is currently exploited in polysaccharide research partly due to the limitations in terms of suitable reaction media. Promising homogeneous synthesis approaches were studied in academia, but conversion into commercial routes is still lacking behind the potential. Moreover, chemical derivatisation (both in academia and industry) has mostly focussed on cellulose and a few other polysaccharide, e.g., starch, chitosan, and dextran (Fan & Picchioni, 2020; Kostag, Gericke, Heinze, & El Seoud, 2019; Nicolle, Journot, & Gerber-Lemaire, 2021). Nevertheless, new sources of polysaccharides have been (re)discovered, and their value in the context of polysaccharide chemistry and material development has been recognised.

6.1.2. Expected achievements and developments in the next 20 years

In the next 20 years, it is expected and demanded that fossil-derived polymers in our daily life need to be replaced. Chemical modification of polysaccharides will provide novel and innovative materials with properties that are specifically tailored for applications in many areas, as described in this document.

The exploration of sophisticated organic synthesis concepts (e.g., *modular synthesis*, *click chemistry*, and *green chemistry*) and homogeneous reaction media (e.g., advances in ionic liquids, low-melting organic salts, and aqueous systems as polysaccharide solvents) as methods to chemically modify polysaccharides will expand, thus, providing access to yet unknown routes for the chemical derivatisation of polysaccharides. Recently emerged trends in this respect will definitively intensify in the upcoming decade (Geng, Shin, Xi, & Hawker, 2021; Morais et al., 2020; Sheldon, 2018; Zou et al., 2018). Another innovative aspect that will see a strong increase in research activities will be the utilisation of novel types of polysaccharides for chemical derivatisation that are available in large quantities yet currently neglected in polysaccharide chemistry, such as polysaccharides from marine sources. e.g., seaweed polysaccharides, biotechnological processes, e.g., fermentation, microalgae cultivation, and waste material valorisation, e.g., by-products from wood such as polyoses, crops, food processing (Chudasama, Sequeira, Moradiya, & Prasad, 2021; Reddy Shetty, Batchu, Buddana, Sambasiva Rao, & Penna, 2021). Thus, a significant impact can be expected by transferring the current knowledge from chemistry applied to cellulose and simple polysaccharides such as starch, chitosan, and dextran to other or even new types of polysaccharides starting materials.

An increasing number of polysaccharide derivatives and synthesis procedures will transition from academia into commercial products due to the general advances in the field of polysaccharide research (e.g., improved synthesis, novel highly desirable materials) as well as changing perspectives on sustainable biobased materials in general. Tackling the limitations of homogeneous synthesis at commercial scales (in particular solvent recycling) is going to be one of the major challenges in commercial polysaccharide chemistry. Access to homogeneous reaction conditions for polysaccharide chemistry will open avenues for other methods and techniques successfully applied in small molecule chemistry, such as, for example, flow chemistry, automated synthesis, and consequently large-scale production, especially for high and medium value-added applications. However, this is not restricted to the context of chemical derivatisation of polysaccharides, but it is also closely related to polysaccharide shaping (in particular fibre spinning) and fractionation of polysaccharides from biomass. Both of which will be major driving forces for the development of novel as well as the improvement of current polysaccharide solvent systems. Based on current trends, it can be stated that the pro & con assessment of heterogeneous *vs.* homogeneous polysaccharide chemistry will shift in the upcoming years in favour of the latter. Highly efficient chemical and chemo-enzymatic methods, including catalysis, for modification of polysaccharides will be adapted from organic chemistry and synthetic polymer chemistry into polysaccharide research for access to defined uniform structures in order to obtain biobased materials with well-defined physical, chemical, and biological properties for advanced applications and model compounds for structure-property-relationship studies (Smith et al., 2020). The development of novel types of semi-synthetic polysaccharide derivatives (e.g., polysaccharides modified with mono−/oligosaccharides or peptides, all-polysaccharide-*co*-polymers) will yield novel, highly engineered polysaccharide-based materials with a huge application potential, especially in the health and personal care sector (Volokhova, Edgar, & Matson, 2020).

The development of polysaccharide-based materials cannot proceed without new methods and technologies to characterise and specify the new materials on a molecular, supramolecular, and macroscopic level. Therefore, known analytical methods will see constant improvements and novel ones will be developed or transferred to the field of polysaccharide research.

6.1.3. *Required research activities*

The transition of novel efficient synthesis approaches from academia into commercial products, and large-scale production is one of the most important issues that needs to be tackled in the near future. It is fuelled by the increasing public demand for biobased materials that are sustainable yet likewise affordable and highly functional. In order to successfully implement sustainability goals, interdisciplinary research efforts with significant industry contributions need to be promoted in order to approach this challenging task from different angles. Automated large-scale industrial production of defined and homogeneous polysaccharide materials with consistent quality is an indispensable requirement, which will be based on the aforementioned achievements.

Advanced characterisation of polysaccharides and polysaccharide-based materials is an integral part of academic and applied polysaccharide research, from biomass fractionation over chemical synthesis to routine quality control, from the elucidation of structure-property-relationships to the development of new biomaterials. Understanding the complex interaction of physical-, chemical-, and biological properties of polysaccharides along all hierarchical levels (from the molecular structure of the individual repeating units and polymer chains to their assembling along the nano-, micro-, and macro-scale) must become a key priority for the development of innovative new bio- as well as biobased materials. This will require scientific and technological advances in different areas, including chemistry, analytics, and process engineering.

The development of task-specific biobased materials makes it necessary to synthesise ever more refined and homogeneous polysaccharide model compounds that are currently unavailable. Key chemical synthesis tools in this regard are protecting group and protecting group-free strategies for regioselective polysaccharide derivatisation, and catalysis as well as chemical/enzymatic synthesis of oligomers/polymers/*block-co*-polymers with highly defined substitution pattern along the chain starting from mono/disaccharide precursors. These sophisticated methods need to be employed and adapted to create tailored model compounds that are required to establish comprehensive structure-property-relationships in different areas and to elucidate highly complex open questions such as the interaction between biopolymers (polysaccharides, lignin, proteins) in native biocomposites (e.g., wood, grasses, plant/animal cell walls). The answers to these open questions will contribute to creating new biocomposites with advanced and engineered functionality.

Purification methods need to be developed. Therefore, modern chromatographic techniques, such as different iterations of field flow fractionation that are currently only used for synthetic polymers, will require implementation for the separation and characterisation of mono-, oligo, and polysaccharides (both in routine methods and advanced academic research).

The constant improvement of analytical methods and tools and the influx of new concepts such as AI-based modelling, learning, and analysis must find their way into the field of polysaccharide research. Solid state and liquid state NMR spectroscopy are very important tools for analysing polysaccharides in their native state (e.g., in wood biomass), after processing (e.g., fibres, nano-assemblies), and after chemical modification (polysaccharide derivatives). However, advances in innovative biomaterial design leads to ever more complex questions and complex structures on a molecular level and the need for even shorter measurement times. Thus, it is necessary to fully implement the technological evolution of NMR spectrometer (e.g., increasing magnetic field strength, novel mathematical models, development of pulse methods) and the recent introduction of advanced methods such as dynamic nuclear polarisation surface enhanced NMR spectroscopy in polysaccharide research.

6.2. *Biology*

6.2.1. *Current challenges*

Over the last decade, we have witnessed spectacular technological advances with ever more accurate and cheaper methods for sequencing genomes and metagenomes, for transcriptome analysis (e.g., using single-cell RNA seq), genome-wide analysis of epigenetic landmarks, proteomics, lipidomics, and metabolomics (Jamil et al., 2020). This is paralleled by extremely efficient and precise methods for genome editing using CRISPR-Cas9, which allow the introduction of almost any genetic change into genomes of almost any organism, including plants (Nasti & Voytas, 2021). Cell biology has been revolutionised with the improvement of the spatial resolution of light microscopy using super-resolution imaging and temporal resolution of observations using genetically encoded sensors and optogenetics, i.e., the use of light to manipulate cellular parameters (Goglia & Toettcher, 2019; Khater, Nabi, & Hamarneh, 2020; Kim, Ju, Lee, Chun, & Seong, 2021). Another rapidly evolving area is the application of soft matter physics in cell biology with the study of liquid-liquid phase separation and the formation of membrane-less organelles and their role in cellular metabolism and signalling (Shin & Brangwynne, 2017). These approaches will also be relevant for the understanding of *in vivo* properties of polysaccharides (Haas, Wightman, Peaucelle, & Höfte, 2021). Structural biology is also undergoing a revolution with the use of cryogenic electron microscopy to resolve structures of multiprotein complexes and of machine learning for highly accurate *ab-nihilo* 3D structure prediction, for instance, by using the Alphafold software (Jumper et al., 2021; Purushotham, Ho, & Zimmer, 2020). Finally, enzymology is being revolutionised with the development of microfluidics-based high-throughput enzyme kinetics assays (Markin et al., 2021). All this has led to an explosion of biological data, which can be mined with increasingly sophisticated bioinformatics tools combined with AI.

In contrast, the analysis of polysaccharide fine structures and their functional roles, despite considerable progress in glycomics and the study of glycan-related genetic diseases, is lagging behind that of other macromolecules in particular in plants and algae (Varki, 2017). This is in part due to the polydispersity as well as the complexity of polysaccharides and the heterogeneity in distribution patterns of side branches, but also to the difficulty of purifying intact polysaccharides and chemically synthesising them.

6.2.2. *Expected achievements and developments in the next 20 years*

Over the next 20 years, major advances are expected in the inventory of natural polysaccharide structures, our understanding of the fine structures on the molecular level of polysaccharides and their relation to functional properties *in vivo* and in the context of material applications. This will rely on new efficient methods for fine-structure determination of polysaccharides and our ability to produce polysaccharide structures of defined degree of polymerisation and branching pattern using novel chemo-enzymatic procedures harnessing a combination of *in vivo* and *in vitro* synthetic biology (Jamil et al., 2020).

We will have learned from studying natural assemblies how to align and pack polysaccharides to design fibres that mechanically outperform silk and nylon and show desired structural colours. We will have acquired the concepts and tools to predict the phase separation behaviour in mixtures of interacting polysaccharides and proteins and to exploit this to produce new materials or biologically active compounds (Sing & Perry, 2020). We will benefit from cost-effective and sustainable large-scale production systems of polysaccharides and fibres. These can be extracted as coproducts from selected food and feed crops, trees, or algae or from dedicated feedstocks cultivated on marginal land to limit competition with food and feed production (Clifton-Brown et al., 2019).

6.2.3. Required research activities

New sensitive and efficient methods for the analysis of polysaccharide fine-structure, e.g., based on MS profiling, glycan arrays, and nanopore sequencing, as well as methods for the study of interactions of polysaccharides with other polysaccharides or ligands, need to be further developed. Methods need to be developed for the in situ analysis of the cell wall architecture at a nanometer scale based on super-resolution microscopy combined with anti-glycan nanoprobes and methods to measure micro-rheology and -mechanics of intact cell wall assemblies.

Collections of plants and algae adapted to a variety of environments need to be screened for new polysaccharide structures. Moreover, methods need to be further developed for the accelerated domestication of wild plants producing polysaccharides or fibres of interest or for the genetic selection or engineering of cultivated plants with improved yields or extractability of desired fibres or polysaccharides.

Polysaccharide biosynthetic pathways need to be elucidated using multidisciplinary approaches, including omics data mining, AI, molecular genetics, cell biology, and structural biology, combined with miniaturised analysis of polysaccharide structures and assemblies. The elucidated polysaccharide biosynthetic pathways need to be reproduced in heterologous systems or *in vitro* using synthetic biology and adapted for large-scale production. These studies will be carried out in model systems, but with improved tools for genome editing, this will be increasingly done on crop plants.

Carbohydrate active enzymes (glycosyl transferases, glycoside hydrolases, glycosynthases, carbohydrate phosphorylases, or other carbohydrate processing enzymes) in microorganisms and plants need to be identified and functions need to be assigned to enzymes through heterologous expression and enzymology. Databases need to be established as training sets with the goal of predicting enzymatic activity from a sequence. These enzymes need to be further improved through *in vitro* evolution by selecting for novel properties adapted to industrial processes. e.g., improved synthase *vs.* hydrolase activity, substrate preferences, catalytic activity, stability, and compatibility with solvents.

6.3. Physics

6.3.1. Current challenges

In the polymer physics perspective, polysaccharide chains behave differently from those of most of the classic bulk polymers, like polyolefins, polyesters, or nylons. The physical properties of classic polymers can be understood based on tight polymer coils, i.e., entropic springs where the stiffness is controlled by temperature, as well as on the entanglements of the coils. By contrast, polysaccharide chains are typically relatively rigid. They are worm-like based on the less flexible saccharide rings in the repeating units. The chain rigidity changes profoundly the behaviour, e.g., how the chains coil and entangle, which, in turn, changes the mechanical and flow properties. But equally importantly, the polymeric repeating units of polysaccharides contain a dense set of hydroxy groups leading to strong interchain physical interactions. However, the individual hydrogen bonds are weak, which makes it challenging to design, for example, sufficiently highly binding plasticising molecules to promote the processibility and rheology. However, the mutual arrangements of hydroxy groups along the polymer chains can allow synergism for complex binding motifs. Also, the hydroxy groups make the properties water sensitive. So, these aspects must be considered when trying to understand the physical properties of polysaccharides.

Polysaccharides have been used in numerous applications, such as in food, gels, paints, and in medical fields. A deeper understanding of the physical properties of polysaccharides is crucial for understanding and tailoring performance of materials derived from these biopolymers. The specific semirigid polymer chain conformations have allowed new properties, such as strain-stiffening in hydrogel networks where the stiffness of the gel increases upon mechanical deformation. This is relevant, e.g., for tissue culture applications to mimic extracellular matrix environments where the biological fault tolerance is promoted by strain stiffening. Cellulose-based fibres have long been used in textiles. One problem involves challenges in identifying common and safe solvents. However, the recent findings in cellulose fibres suggest new and more benign solvent media based on ionic liquids for cellulose but also for polysaccharides in general. Therein, interactions between the solvent and polymer chain can be highly subtle to design and understand and can require careful modelling due to the complexity of the problem.

Various polysaccharides have already been considered as alternatives for fossil-based polymers. Therein the semirigid chains in a combination of the hydrogen bonds and water sensitivity posed challenges. Numerous approaches have been presented to plasticise the polymers to allow melt-processing, whereas the landmark findings are, however, still awaiting. As an alternative approach, polysaccharides have been used as additives within thermoplastic polymers in blends and (nano)composites, notably nanocelluloses within biodegradable matrices. Importantly, various forms of colloidal level nanocelluloses have recently been maturing to be technically and economically feasible to allow reinforcement in blends, spinning fibres, and allowing structural colours. As a remarkable state of the art, one can mention the Japanese *Nano Cellulose Vehicle* to demonstrate the technology readiness level.

6.3.2. Expected achievements and developments in the next 20 years

Polysaccharides and polysaccharide-based materials will have relevant applications in several specific functional applications. It is expected that deeper and fundamental understanding of their physical properties (e.g., solubility, rheological behaviour, optical/electrical/mechanical properties) will be gained. This will have a huge impact on the development of new processing strategies and biomaterial design. In the context of the energy storage and energy efficiency, one can foresee all-polysaccharide batteries and supercapacitors, also utilising lignin, as well as polysaccharide components in solar cells. This is suggested by the promising results on the complex physicochemical interaction between different types of polysaccharides as well as between polysaccharides and other biopolymers (e.g., proteins, lignin). Light-weight construction based on nanocellulose reinforcements is expected to gain application potential in specific technical applications. It exploits the versatility of nanocellulose compounds, ranging from reinforced nanocomposites and optical transparency to rigid and elastomeric composites. Comprehensive evaluation of polysaccharides in the context of polymer physics will benefit from the advances made in the field of synthetic macromolecules, resulting in novel biomaterial developments. As an example, polysaccharides will have growing relevance in tissue culture and medical sciences due to their biological compatibility but also due to their specific worm-like semirigid chain conformation. It is also expected that optical properties of native polysaccharides, chemically modified polysaccharide derivatives, and materials obtained therefrom can be mastered to allow, e.g., optical fibres and devices for sensing and biomedical applications. Novel insulation and flame-retardant materials will be developed that take advantage of fundamental studies on the thermal-, electrical-, and acoustic conductivity within polysaccharide-based foams and aerogels. The understanding of structural colours of cholesteric polysaccharide assemblies and nanocellulose liquid crystals is foreseen to mature for applications. We also foresee that disordered modified polysaccharide networks will allow to obtain sustainable white pigments that can replace hazardous metal oxide pigments in coatings and paints.

Dissolution of polysaccharides is indispensable for their processing (e.g., shaping, extraction from biomass, homogeneous chemistry). Significant advances are expected in understanding and predicting the solubility and insolubility of cellulose and other polysaccharides in aqueous and organic solvent media (Etale, Onyianta, Turner, &

Eichhorn, 2023; Mark, Xinzhong, Changlu, & Lianzhong, 2017; Norgren et al., 2023). Ultimately, this will enable the development of tailored polysaccharide solvents for different purposes.

6.3.3. Required research activities

Comprehensive physicochemical and theoretical studies are needed to fully understand the thermodynamic and kinetic principles of the dissolution of polysaccharides in aqueous and non-aqueous solvents. Finding answers to fundamental questions such as “Why are polysaccharides like cellulose insoluble in water and common organic solvents?”, “What is the influence of hydrophilicity, hydrophobicity, crystallinity, hydrogen bonding, entropic effects, and other parameters on the dissolution process?”, and “How can we exploit this knowledge to develop task-specific solvents for different polysaccharides and different applications?” will be crucial for advancing polysaccharide research in the next decades. Studying the interaction of polysaccharide-based materials with water is also important in this context, e.g., to reduce their sensitivity to moisture. Being a complex physical problem that involves an interplay of many parameters, it is expected that machine learning and AI could allow tools to find solutions. This requires major new approaches and agreed protocols to construct large data libraries.

Another major aim is that polysaccharide-based materials could growingly replace bulk polymers in applications presently dominated by fossil-based polymers, such as polyolefins, polyesters, and nylon, by exploiting waste streams in a circular economy. To this end, major developments are needed in several fields. To facilitate seamless market entry for bulk applications, polysaccharides should allow melt processing with the existing devices in the polymer industry with as small as possible modifications, such as extruders and injection moulding devices. This requires thermoplasticity based on tailorable rheology as a function of temperature. Even if considerable progress therein has already been recently made, fundamental research is needed to understand and tune the chain dynamics and interactions of polysaccharides and polysaccharide derivatives as the polymer chains are typically relatively rigid, also involving a multitude of hydrogen bonding interactions. The typical avenues are chemical side chain modifications or identification of suitable plasticisers. The latter approach is, in principle, highly attractive as, in this case, the biobased polymers require no modification. Developing truly versatile plasticisers will require fundamental understanding of their molecular interaction with polysaccharides, their diffusion properties in extended polysaccharides matrices (in order to prevent leakage), as well as the tailored control over chain dynamics and excessive polymer aggregation (in order to tune the thermoplastic properties). Such approaches are also critical to achieve toughness in mechanical deformations, i.e., to suppress catastrophic failures in technical applications. Also, the physical basis of promoted ductility of worm-like chains needs to be refined.

The polymer physics of semirigid polymers in general and polysaccharides in particular need to be further developed to understand their structural and rheological properties. This also requires multiscale simulations and models to design functionalities and properties and how to balance the strong intramolecular interactions with sufficiently repulsive groups allowed by plasticisers or grafted groups. From the physics perspective, a specific need is to develop rational routes for polysaccharide self-assemblies for controlled and useful nanostructures. In classical polymers, the self-assemblies are typically achieved using various architectures of block copolymers, where living polymerisation strategies have been developed over the recent decades. They allow narrow molecular weight distributions and copolymerisation of different polymer blocks in different architectures. Totally different physical, chemical, and biological strategies must be developed for polysaccharides. The first challenge is to achieve narrow polydispersity, which may be challenging to obtain simply from the naturally obtained polysaccharides by chopping. The *block*-like polysaccharide structures may have to be constructed by end-to-end linkages of low molecular weight precursors or polymers. This requires mastery of topochemical end group reactions. Synthetic biological concepts need to be developed for well-defined polysaccharides and their block copolymer-like self-assemblies.

Research is needed to construct polysaccharides with novel functions such as optical/barrier/separation properties, electrical conductivity or insulation, and flame retardancy. This will require new ways to modify refractive indices, incorporate ionically or electronically conducting moieties, either chemically or supramolecularly. Moreover, it needs to be studied how advanced functions and physical properties are controlled by a defined (nano)structure over different length scales and hierarchies. Therein, it is expected that exploiting plant-based structures such as wood could serve as templates. Hints for this approach have already been shown, e.g., bullet-proof compacted wood as well as highly conducting polysaccharide-based electrolytes.

A very complex and important aspect that needs to be understood is the correlation between physical properties and the structural perfection/imperfection of polysaccharide-based materials. As an example, highly controlled nanocelluloses can be obtained based on subtle processes and well-defined sources. However, economical aspects may suggest using less expensive processes and less-controlled source material, notably waste streams. The ultimate question relates to understanding the relations between structural perfection and achievable properties.

The research activities in the development of new methods and techniques for polysaccharide chemistry, biology, and physics will be triggered by the identification of the needs of society and environment. Targets and demands will be identified, and together with tailored polysaccharide materials, will be accessible by application of the methods and approaches developed in fundamental research.

7. Skills and education systems needed towards 2040 goals

To date, professionals in biopolymers and polysaccharides are educated within degree programs in engineering and science subjects that equip the students with skills in physics, chemistry, biology, processes, technologies, and product solutions. The prospect for the next 20 years is that these professionals will, in addition, need to master framework skills that include knowledge of material circularity, life cycle, and socio-economic impact analyses. The framework topics of sustainability, circularity, and economics will become integral in the degree programs.

By 2040, the education of professionals in biopolymers and polysaccharides will become more connected in Europe. This will be facilitated by a virtual education platform that unites academia, industry, and the general public and by an iterative system to assess and validate key competencies and skill gaps for current and future needs. An educational system that provides professionals to Europe that are skilled in science and engineering as well as in framework skills will be in place. Digital education, mobility and inclusive and connected higher education will be the critical tools to reach the high-quality education landscape within science and engineering areas, such as biopolymers and polysaccharides.

7.1. Current challenges

The topics of biopolymers and polysaccharides are interdigitated in education in degrees in Materials Science & Engineering, Food & Nutrition, and Biomedical, Chemistry, Biology & Physics (Fig. 6). Master of Science degrees in biorefinery, food, and pulp and paper encompass polysaccharide topics, while degrees in chemistry and physics include the molecular and phenomenological principles applicable to the field of polysaccharides. Currently, there is no degree program dedicated specifically to biopolymers or polysaccharides in Europe. Institutions qualified by the European University Charter offer various modules dealing with biopolymers and polysaccharides. Examples of module themes taught at master level in English are:

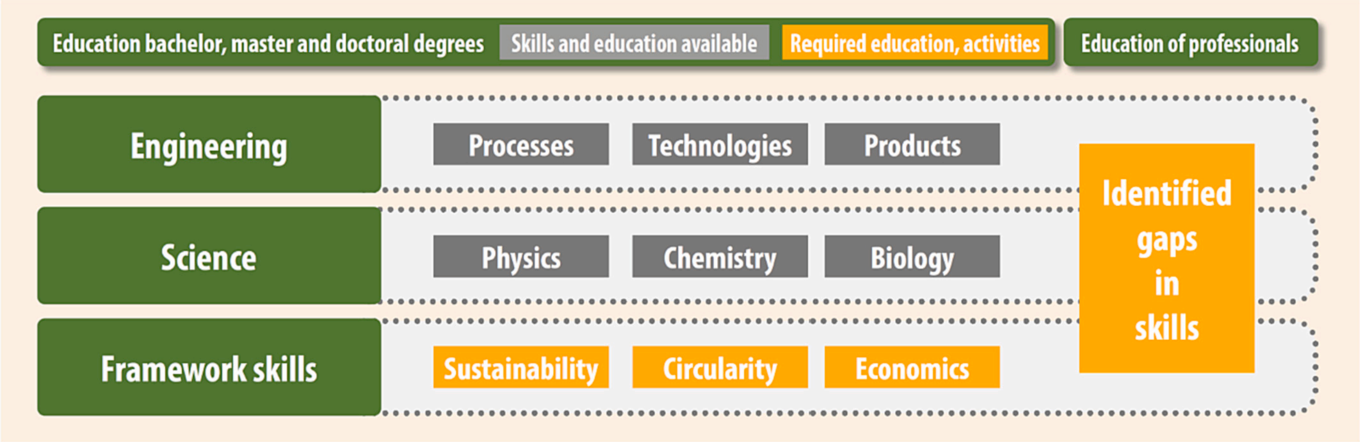

Fig. 6. Schematic overview of the different education programs required for enabling skills needed for future biopolymer and polysaccharide research and engineering in Europe.

- carbohydrate chemistry
- polysaccharide chemistry
- biomass chemistry and technology
- biorefinery
- bioorganic chemistry
- cellulose, wood, and paper technology
- analytical and characterisation techniques for carbon-based materials covering molecular, nano-structured up to macroscopic material level
- biochemistry and biological basics
- spectrum and utilisation of renewable materials
- environmental and ecological basics
- sustainability development goals and circular economy
- waste and emission management

The current degrees and courses in bachelor, master, and doctoral education address the various engineering and science subjects that equip the students with skills in physics, chemistry, biology, processes, technologies, and product solutions (Fig. 6). Education in what we call herein *framework skills*, which include knowledge of material circularity, life cycle, and socio-economic impact analyses, are not systematically embedded in educational programs.

7.2. The vision 2040

In 2040, material use will be shifted towards intentional consumption due to increasing awareness and knowledge of material life cycles and material socio-economic impact. This shift will be largely facilitated by national and European education efforts in science and engineering topics within sustainable and renewable materials, such as polysaccharides. The quality of science and engineering related education will rise, and the education programs will become more connected within Europe. Incorporating the education of framework skills that comprise numerical skills of material circularity, life cycle, and socio-economic impact analyses will contribute to transform the skill set of European graduates. Current critical tools to reach the high-quality education scenery within science and engineering areas, such as biopolymers and polysaccharides, are the EC's European Education Area activities on developing *digital education*, *life-long learning*, and *inclusive and connected higher education*.[5] These promote key competencies such as (i) literacy, (ii) multilingualism, (iii) numerical, scientific, and engineering skills, (iv) digital and technology-based competencies, (v) interpersonal skills, (vi) the ability to adopt new competencies, (vii) active citizenship, (viii) entrepreneurship, and (ix) cultural awareness and expression.

Within the materials and products related bachelor, master, and doctoral education in biopolymers and polysaccharides, the benchmark is knowhow on making materials with targeted quality that matched with the purpose of use and its life cycle. This is facilitated by equipping the professionals with the skills in quantifying the societal, economic and environmental impact of materials and of constructing a sustainable production chain. These are continuous items in the curricula in all degree programs within biopolymers and polysaccharides. The technical competencies of students at bachelor and master levels have risen benefit of progress in the digitalisation of education. In science and engineering education, the use of digital teaching tools such as virtual laboratories that combine simulation, analysis, and calculations of societal, economic, and environmental impact, has been central in the skills development of the professionals. New tools in all degree programs have emerged that make use of digital tools for experimental design and predictive simulations to minimise training for the trial-and-error type of problem-solving.

The students in science and engineering fields are enrolled to home universities. However, the ECs initiative for inclusive and connected higher education has facilitated an education horizon that is not limited to the home universities.[5] The connectedness of European education scenery is further made possible by topic networks, such as EPNOE, in the field of biopolymers and polysaccharides that bring together students from European countries and universities to work within a specific context but approach it from diverse application areas and socio-economic backgrounds. The topic networks have been transitional also for the education of postgraduates and professionals in working life.

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[5] European Education Area, Focus Topics, Digital Education, Digital action plan (2021–2027), https://education.ec.europa.eu/focus-topics/digital/education-action-plan;European Education Area, Focus Topics, Improving Quality, Council Recommendation on Key Competences for Lifelong Learning; https://education.ec.europa.eu/focus-topics/improving-quality-equity/key-competences-lifelong-learning;European Education Area, Education Levels, Inclusive and connected higher education, https://education.ec.europa.eu/education-levels/higher-education/inclusion-and-connectivity.

Educating professionals and maintaining the skills of graduates working in the industry is used to circle back their competence to education (Fig. 6) and make it possible to iteratively identify skill gaps for the current and future needs of Europe. In the context of biopolymers and polysaccharides, an ambitious goal needs to be achieved by 2040: "A fully implemented educational system that provides professionals to Europe that are skilled in science and engineering as well as framework skills."

7.3. Tools for enabling the vision

It is essential to combine the EC's education initiatives (e.g., digital education, key competencies, and inclusive and connected education in Europe) with the aims and opportunities of topic specific scientific and engineering focussed networks (such as EPNOE in the fields of biopolymers and polysaccharides). Only then can the vision of a European education that is connected, inclusive, and of high quality become reality. Vital tools to (a) facilitate connectedness, high quality, and inclusiveness as well as (b) promote education in biopolymers and polysaccharides at the different professional stages are:

- mobility and training programs (e.g., ERASMUS+, Horizon Europe, Marie Skłodowska-Curie Actions, COST – European Cooperation in Science and Technology, CEEPUS – Central European Exchange Programme for University Studies)
- activities that strengthen cooperation between the different levels of educational institutions, research institutions, and companies
- employment of virtual tools that promote inclusiveness and accessibility of education
- virtual education platform that unites academia, industry, and the general public
- iterative systems to assess and validate key competencies and skill gaps for current and future needs

8. Summary & conclusion

Polysaccharides are abundantly available polymeric materials of today and tomorrow. Future sustainable materials based on polysaccharides will emerge for numerous targeted applications in engineering, materials science, food and nutrition and biomedical fields. In the context of a more sustainable planet and a more efficient circular economy, polysaccharides are very well-positioned to transition from fossil-based to sustainable biobased materials with equal or improved performances. The next generations of polysaccharides will find inspiration in nature in the attempt to mimic both form and function. The use of functional composites from sustainable and renewable resources will be pivotal in our future industrial practices. Polysaccharides can be used both as a continuous or a dispersed phase. The current increased digitalisation and continuous development around internet-of-things must be combined with sustainability. Polysaccharides will be strategic components for energy storage and harvesting, replacing fossil-based products for a wide range of industrial applications. Processing of polysaccharides must be economical and environmentally competitive. Although polysaccharides might appear as an inexhaustible resource, it is important to identify and study the available feedstock in relation to the techno-economical perspective for each specific product and application to enable a sustainable production. Interdisciplinarity combined with the sustainable and circular economy should be a general approach to advance.

Polysaccharides play a pivotal role in human nutrition and food structure design. Starches, being the major source of nutritional carbohydrates, were and remain to this date the prime focus of the research effort. However, the last two decades saw a growing interest in complex oligo- and polysaccharides and their assemblies that are not digestible by human enzymes. These types of carbohydrate materials are classified using the umbrella term *dietary fibre*. Importantly, dietary fibre influence macronutrient digestibility and impact systemic, whole-body metabolism through a chain of events that begin with delaying gastric emptying and proceed to colonic fermentation of dietary fibre by the gut microbiome. Within the strategic horizon of the next two decades, a more detailed understanding of the structural characteristics and structure-function-relationships of dietary fibre will afford the development of targeted dietary fibre with programmable interactions, rheological properties (gelling, viscosifying), physiological response (fermentability, immune modulations), as well as techno-functional properties to benefit public health and sustainable food processing and manufacturing. This progress in understanding will require highly advanced analytical techniques based on chemical microscopy, NMR, and MS, for example.

The inherent biological and pharmacological activities, biocompatibility, biodegradability, distinctive physical and chemical properties of polysaccharide, and the versatility of their derivatives, have been extensively exploited to create biomaterials and medicinal products applied to clinical practice, under clinical trials or *in vivo* experiments. The scientific and biotechnological interest devoted to polysaccharides in biomedicine conflates five principal topics of research: (i) bioactive polysaccharides, (ii) cosmetics, (iii) drug delivery and nanomedicine, (iv) medical devices, and (v) tissue engineering and regenerative medicine. Within the strategic horizon of the next two decades, innovative clinical applications, processability, performance improvement, market introduction, and future perspectives of next-generation polysaccharide biomaterials will emerge, such as the development of new targeting agents and smart carriers for drugs, medical devices with anti-inflammatory, anti-infective, and anti-coagulant activities and expansion of emerging therapeutic applications on *in vitro* disease modelling, and microtissue formation and maturation. The toolbox of polysaccharides available and their inherent characteristics establish a comprehensive range of opportunities for the synergistic development of innovative systems. We expect these examples may outline future directions in biomedicine and biotechnology, which will expedite the clinical use of natural polysaccharide materials and prospect manufacturing and analysis processes.

Novel techniques and methods in chemistry, biology, and physics will provide innovative polysaccharide-based materials with defined properties on the molecular level that are specifically tailored for emerging applications. In the next 20 years, a demand with high priority for society as well as politics is the replacement of fossil-based products and synthetic polymers derived therefrom in our daily life needs. In line with sustainability, protection of resources, and most importantly, care for the environment in all aspects, polysaccharides from renewable resources are most suited to fulfil this role. A few examples of necessary actions and opportunities in these three major areas are described below. In chemistry, we envision the adaptation of highly efficient chemical and chemo-enzymatical synthesis into polysaccharide research and the development of methods for the fabrication of novel types of semi-synthetic polysaccharide derivatives, well-defined all-polysaccharide-*co*-polymers, and combined co-polymers of polysaccharides with other biopolymers such as polypeptides for advanced applications. In biology, we foresee the production of polysaccharide assemblies of defined molecular structure (in particular regarding the degree of polymerisation, polymer backbone, and branching pattern) using novel chemo-enzymatic procedures harnessing a combination of *in vivo* and *in vitro* synthetic biology, elucidation of polysaccharide biosynthetic pathways using multidisciplinary approaches and the development of methods for the *in situ* analysis of intact biological assemblies at a nanometer scale. In physics, we envisage the development of fundamental research to tune the chain dynamics and interactions of polymer chains in polysaccharides and machine learning and AI for finding solutions based on new approaches and agreed protocols constructed in large data libraries. The concerted research activities will be triggered by the identification of the needs of society and environment - targets and demands will be identified, and tailored polysaccharide-based materials fabricated by the developed methods and techniques fulfilling the requirements will be applied.

Professional skills in biopolymers and polysaccharides are educated within degree programs in engineering and science subjects that equip the students with skills in physics, chemistry, biology, processes, technologies, and product solutions. The prospect for the next 20 years is that these professionals will, in addition, need to master framework skills that include knowledge of material circularity as well as life cycle and socio-economic impact analyses. The framework topics of sustainability, circularity and economic will become integral in the degree programs. In 2040, education will have changed substantially, and this will include the fields of biopolymers and polysaccharides. Most notably, it will have become much more connected within the European community. In order to facilitate this vital transition, virtual education platforms need to be developed sooner rather than later that unit academia, industry, and the general public.

CRediT authorship contribution statement

Martin Gericke: Writing – original draft, Writing – review & editing, Conceptualization. **Adérito J.R. Amaral:** Writing – original draft. **Tatiana Budtova:** Conceptualization, Writing – original draft. **Pieter De Wever:** Writing – original draft. **Thomas Groth:** Conceptualization, Writing – original draft. **Thomas Heinze:** Conceptualization, Writing – original draft. **Herman Höfte:** Conceptualization, Writing – original draft. **Anton Huber:** Conceptualization, Writing – original draft. **Olli Ikkala:** Conceptualization, Writing – original draft. **Janusz Kapuśniak:** Conceptualization, Writing – original draft. **Rupert Kargl:** Conceptualization, Writing – original draft. **João F. Mano:** Conceptualization, Writing – original draft. **Már Másson:** Conceptualization, Writing – original draft. **Pietro Matricardi:** Conceptualization, Writing – original draft. **Bruno Medronho:** Writing – original draft. **Magnus Norgren:** Conceptualization, Writing – original draft. **Tiina Nypelö:** Conceptualization, Writing – original draft. **Laura Nyström:** Conceptualization, Writing – original draft. **Anna Roig:** Conceptualization, Writing – original draft. **Michael Sauer:** Writing – original draft. **Henk Schols:** Conceptualization, Writing – original draft. **John van der Linden:** Writing – original draft. **Tanja Wrodnigg:** Conceptualization, Writing – original draft. **Chunlin Xu:** Conceptualization, Writing – original draft. **Gleb Yakubov:** Conceptualization, Visualization. **Karin Stana Kleinschek:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Pedro Fardim:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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