Article

Biosynthesis, applications, and mathematical modeling dynamics of lactic acid bacteria exopolysaccharides: A review

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Abstract

There is a dearth of literature on mathematical modeling for producing exopolysaccharides (EPS) synthesized by lactic acid bacteria (LAB). Mathematical models can enhance EPS yield by considering the distribution of control over metabolic flows and physicochemical restrictions. These models improve the economic viability of LAB-EPS production by optimizing output and reducing substrate use. White-box models, utilize comprehensive system knowledge, forecast performance, and optimize processes such as EPS biosynthesis while employing algorithms like fuzzy patterns, rule-based systems, and decision trees to increase productivity and identify bottlenecks. Stoichiometric models quantify the relationship between substrate consumption and EPS production, optimizing carbon fluxes. Metabolic and pathway-based models provide data regarding intracellular networks governing EPS biosynthesis and the effects of nutrient availability. Global models, such as flux balance analysis (FBA), integrate genome-scale networks to predict cellular behavior and optimize production conditions. This review highlights the utility of mathematical modeling as a technique for augmenting LAB-EPS production, discussing various modeling approaches that offer insights into modifying EPS's physicochemical characteristics, structure, and functions. These models can aid in upgrading manufacturing processes, enhancing scalability, and improving the efficiency of LAB-EPS research. The review emphasizes the role of mathematical modeling in optimizing EPS production for applications in the cosmetics, food, dairy, and pharmaceutical industries and strategies to improve industrialscale processes.

Keywords exopolysaccharides; lactic acid bacteria; biosynthesis; eps applications; mathematical modeling.

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1 Introduction

In recent times, there has been a renewed inclination towards the manufacture of exopolysaccharides (EPSs) by microorganisms owing to the rising requirement of natural polymers for diverse industrial uses. EPS's are

described as naturally occurring high molecular weight polymeric substances that are secreted by the microorganisms outside their cell structure in the environment (Kanmani et al., 2011; Mehta et al., 2023; Staudt et al., 2004). They either exist as a loosely attached slime layer (ropy EPS) or a securely bound capsule (CPS) (Zeidan et al., 2017). Due to the inherent properties of producer microorganisms such as faster growth cycles, high yield, and controlled production capabilities, microbial EPS can replace plant-based and algalbased EPSs. Owing to various compelling physicochemical and rheological characteristics, coupled with novel functionality, biocompatibility, and non-toxic nature, the EPSs function as novel biomaterials in various industrial sectors such as textile, detergent, medicine, adhesive, wastewater treatment, brewing, microbial enhanced oil recovery (MEOR), downstream processing, cosmetic, food additives, and pharmacology (Freitas et al., 2017; Nambiar et al., 2023; Özcan & Öner, 2015; Rühmann et al., 2015). Among the bacteria that can produce EPS, LAB has bragged the attention of researchers due to their strong capability to synthesize EPS along with its GRAS (Generally Recognized as Safe) status. LAB are gram-positive rods or cocci that are nonspore-forming, acid-tolerant, have a low GC content, lack catalase activity, and can thrive in anaerobic or microaerophilic environments. They are particularly well recognized for their capability to ferment sugar into lactic acid (Ansari et al., 2023; Nicolescu et al., 2023; S. Patel et al., 2012). LABs are widely employed in medicine, dairy products, biotechnology, and industrial fermentation as a starter culture (Bajpai et al., 2015). They play a vital role in health complications and contribute to the growth of beneficial microflora in the intestine (Kim et al., 2010), along with the capability to produce functional EPS. The ecological role of the EPSs produced by LAB is not well understood and is likely complex, even though it resembles to be associated with cell adhesion and cell protection in numerous scenarios (Ruas-Madiedo et al., 2002; Werning et al., 2022). The majority of LAB manufacture HePS, which is typically made up of L-rhamnose, D-glucose, and D-galactose (Notararigo et al., 2013). The intracellular glycosyltransferases are responsible for converting sugar nucleotides into these polysaccharides. Other LAB generates HoPS that solely include D-glucose (such as levan and inulin) or D-fructose (such as dextran, reuteran, and mutan) the process of which will be discussed further in the review. Extracellular glycan-sucrases (glucan- or fructan-sucrases) often use sucrose as the glycosyl donor to synthesize HoPS. It has been recorded that glycansucrases cause EPS production in strains of the Lactobacillus (Bivolarski et al., 2021; İspirli et al., 2019; Vasileva et al., 2017), Leuconostoc (Dai et al., 2024; Tian et al., 2024; Zuo et al., 2024), and *Weissella* species (Hu et al., 2017; Malik et al., 2009; Zhou et al., 2024). The rheology, texture, and "mouthfeel" of fermented milk products(such as yogurt, viili, lángfil, etc.) and other fermented commodities like sorghum sourdoughs rely heavily on the HePS produced by LAB (Notararigo et al., 2013). HoPS producers are mostly utilized for non-dairy product fermentation and have received less exploration. Some of these HoPS synthesizing LAB strains positively affected the dough rheology, and bread texture (Rühmkorf et al., 2012; Sha et al., 2023). In addition to its probiotic capabilities, EPS from LAB has been related to health benefits because of its putative antitumoral, immunostimulatory, and blood cholesterol-lowering effects (Bertsch et al., 2019; Notararigo et al., 2013). Although apart from the total worldwide production data of other EPS produced by LAB is not available in the literature yet due to its niche market more focus on the mainstream products and their high demand. Due to the same reason, the industrial application of EPS isolated from LAB has not been explored much and remains unexplored. The large-scale production of EPS also possesses numerous challenges such as cost of raw materials, specific growth conditions, low amount of EPS produced by LABs, technical challenges faced at the scale-up process, regulatory compliances, and energetics of LABs are such that it is not practical to produce huge amounts of EPS (Nguyen et al., 2020; Rahman et al., 2024; Welman and Maddox, 2003). The growth of particular LAB strains requires the provision of specific growth media and incubation conditions which may increase the cost of production of the product at the industrial level. To overcome this media optimization should be done by

understanding the growth kinetics of the specific stain so that a high yield can be obtained by using biowastes or cheaper components as the media components. The yield can be either increased by using metabolic engineering of the EPS producer strain or by optimization of the incubation conditions and media composition. The regulatory compliances should be met according to the desired product and the region. Mathematical modeling plays a crucial role in the understanding and optimization of EPS produced by LAB. In recent years, it has emerged as a potent tool for the elucidation of the dynamics of synthesis of EPS and its fermentation process. The integration of various principles from different domains such as biology, chemistry, engineering, and mathematical modeling provides a systematic framework for the prediction and optimization of mechanisms that govern the EPS biosynthesis, utilization of substrates as well as metabolic flux distributions with the LAB bacterial isolate. With the aid of computational simulations and sensitivity analyses, the researchers can carry out the identification of optimal fermentation conditions for the higher yield of EPS and increased quality with reduced production costs. Thus, the overall cost of the production at the industrial scale can be lowered with higher yield if mathematical modeling is used as an aid in the production process and the kinetics of the biosynthesis is studied and altered. Thus, the interdisciplinary partnership amongst biologists, mathematicians, engineers, and mathematical modeling holds the capability to unlock the full potential of EPS from LAB in diverse industrial areas which will be discussed later in this review.

2 Types of EPS

Two main classes define EPS categorization namely, Homopolysaccharides (HoPS) and Heteropolysaccharides (HePS), which are determined based on the synthesis mechanism and the main chain's composition. In general, HePSs are created outside of the cell by an enzyme released by the bacterium, whereas HoPSs are composed of only one type of monosaccharide and are synthesized intracellularly. HoPS are grouped into several categories, such as D-glucans, fructans, polygalactans, etc (Angelin and Kavitha, 2020). HePS, however, contains repetitive units of D-glucose, D-galactose, L-rhamnose, etc. The polymers classified as HoPSencompass curdlan, pullulan, dextran, cellulose, scleroglucan, cellulose, and others. Notably, curdlan and cellulose, both linear HoPS, feature 1,3 glucan and 1,4-glycosidic linkages respectively (Jurášková et al., 2022). Scleroglucan and pullulan are examples of branched HoPS that feature 1, 3, and 1, 6 glycosidic linkages, respectively. HePS derived from LAB constitute a subclass of EPS constituted of different monosaccharide units in the sugar polymer chain. They are the end product of the gelation of precursor sugarnucleotide molecules synthesized in the periplasmic region, such as UDP-glucose and UDP-galactose. An EPS biosynthesis cluster, housing glycosyltransferase genes, regulatory genes, as well as those governing chain length determination, polymerization, and export, is conventionally arranged in an operon. This operon oversees the controlled synthesis of EPSs from the aforementioned precursors (Werning et al., 2022). HePS yield and molecular characteristics can be influenced by some factors, which include growth conditions (Temperature, oxygen level, and pH), medium composition (carbon sources and nitrogen sources), as well as incubation period (Lynch et al., 2018). The changes amongst these variables can effectively cause alteration in the synthesis of the polysaccharide formed. The vast diversity in EPS is associated with changes in the monosaccharide's non-sugar decorations, conformation, molecular weight, anomeric configuration, glycosidic linkage, and sugar building blocks (Zeidan et al., 2017) which ultimately relates to different types of HePS serving different applications. The HoPS have a relatively simpler structure thus they can show structural diversity based on glycosidic linkages and branching and thus serve as storage forms of energy or as structural components. In contrast, HePS are more complex due to the inclusion of multiple types of monosaccharide units which provide the capability to possess more structural diverse features owing to its numerous

applications in different sectors whether it be as thickeners, texturizers, or emulsifiers in the food industries, from gelling agent in the pharmaceutical sector to binding agent in the cosmetic industry (Vu et al., 2021).

3 EPSs Produced By Lactic Acid Bacteria

The microorganism's capacity to synthesize EPSs has both advantages and disadvantages. The food industry utilizes polysaccharides derived from plants and seaweeds due to their capacity to thicken and form gels. Compared to plant polysaccharides, microbial polysaccharides have the advantages of controlled production methods in a restricted production time and space, as well as stable chemical properties and continuous market availability. The bacterial EPSs on the other hand are in demand which include xanthan from Xanthomonas campestris (Palaniraj and Jayaraman, 2011) and gellan from Sphingomonas paucimobilis (Sá-Correia et al., 2002) which are used for numerous applications. Such kinds of EPSs are widely used in commercial and industrial applications in aid with various conventional biotechnological processes. However, the distinct physical properties of these EPS restrict their use to be the sole source in every application, and thus a demand arises for novel EPS that can provide rheological, functional as well as nutritional benefits to the product. One of the major issues with bacterial EPSs in the food industry is that not every bacterium is Generally Recognized as Safe (GRAS). Thus, the EPSs isolated from LAB can be a cure for this issue (Sakr et al., 2021). There are numerous LAB genera, including Weisella, Streptococcus, Lactobacillus, Pediococcus, and Leuconostoc (Ruiz Rodríguez et al., 2019). LAB creates a wide range of metabolites, including EPSs, mannitol, bacteriocins, 1,3-propanediol, fatty acids, and organic acids (Garai-Ibabe et al., 2010; Y. Xu et al., 2019). LAB synthesizes a variety of EPS, including HoPS such as polygalactans, dextran, mutan, alternan, reuteran, levan, and inulin-types. HePS such as xanthan, gellan, kefiran, etc., are also produced by LAB (Angelin and Kavitha, 2020). The formation of both HoPS and HePS provides the LAB EPS with a greater extent of structural diversity. The different types of monosaccharide units present in HePS provide them different structural conformations which provide them distinctive applications due to their different structural features. LAB also produces HoPs but they are not structurally complex and thus provide a single type of application mostly either as a storage source of energy or structural components such as cellulose. Several LABs are used frequently in various food applications due to their preservative, functional, therapeutical, antioxidant, and nutritional properties (Table 1). The isolate Streptococcus thermophiles XJ53 demonstrated significant immune activity when proliferation, phagocytic capacities, and nitric oxide (NO) output of macrophage RAW264.7 were subjected to comparative analysis (Xia et al., 2023). Apart from having various applications in the food industry it also has a few cons such as spoilage of beverages, causing allergic reactions in some individuals as well as alteration of the flavor of the product. Apart from this, EPS can serve as an energy source as well as a safe environment for the growth and proliferation of other microorganisms which can be a big issue in large-scale production and can lead to huge economic loss. The physical and chemical properties of the food product may be impacted by how EPS interacts with other food ingredients. Despite these constraints, the potential benefits of LAB-derived EPS in improving food texture, stability, and functioning make it an appealing ingredient in a variety of food applications. Mathematical modeling can help understand the association between LAB EPS structure and functionality, which will be discussed later in the review.

4 Biosynthesis of EPS

The LAB can produce two types of EPS based on their monomeric composition: homopolysaccharides (HoPS) and heteropolysaccharides (HePS).Different types of HoPS and HePS synthesized by LAB have been illustrated in Fig. 1 (Abid et al., 2018). Lactic acid bacteria (LAB) generate extracellular polysaccharides (EPS)

via membrane-bound and cytoplasmic enzymes. The genes responsible for EPS biosynthesis are frequently grouped into operons, which are gene groups that are transcribed simultaneously. These operons usually contain genes for sugar transport, polymerization, and modifying enzymes, and their expression is affected by environmental factors such as carbon sources and fermentation conditions. Thus, the biosynthetic pathways for the synthesis of both HoPS and HePS have been reviewed in this section.



Fig. 1 Types of EPSs produced by lactic acid bacteria.

The diversity of EPS types found in different LAB species reflects these bacteria's capacity to thrive in a variety of ecological contexts, ranging from fermented foods to the human gastrointestinal tract. Understanding EPS's structural variety and functional roles is critical for its use in food, medicines, and biotechnology, where its prebiotic, gelling, and emulsifying qualities are valued.

EPS	LAB	Linkage	Classification	Source	Application	References
	producing EPS					
Dextran	Lactobacillus kunkeei AP-27.	α -1,6 glycosidic linkages in main chain and α -1,2, α	Phylum: Firmicutes; Class: Bacilli; Order: Lactobacillales; Family: Lactobacillaceae	Bee pollen isolate	Act as an emulsifier, adjuvant, and carrier, stabilizer in food and pharmaceutical	(Yilmaz et al., 2023)
	Lactobacillus kunkeei AP-37	-1,3 and α - 1,4 branched glycosidic linkages	Phylum: Firmicutes; Class: Bacilli; Order: Lactobacillales; Family: Lactobacillaceae	Fermented bee products	also be used as plasma substitute, matrix, anticoagulant, paper industry, MEOR and biomaterials.	(İspirli et al., 2023)
	Leuconostoc pseudomesenter oides DRP-5		Phylum: Bacillota; Class: Bacilli; Order: Lactobacillales; Family: Lactobacillaceae	Homemade wine		(Du et al., 2023)
Alternan	Lactobacillus re uteri E81	α -1,6 and α - 1,3 glucosidic linkages, with some α - 1,3 branchings	Phylum: Bacillota; Class: Bacilli; Order: Lactobacillales; Family: Lactobacillaceae	Sourdough	Prebiotics, confectionary sweeteners, low viscosity bulking agents, and food extenders	(Yilmaz et al., 2020)
	Leuconostoc citreum ABK-1		Phylum: Bacillota; Class: Bacilli; Order: Lactobacillales; Family: Leuconostocaceae	Khow-tom- mud (Thai dessert)		(Wangpaiboon et al., 2018)
Levan	Leuconostoc mesenteroides S 81	β -2, 6 glycosidic bonds β -2,1- linkedside chains	Phylum: Firmicutes; Class: Bacilli; Order: Lactobacillales; Family: Leuconostocaceae	Fish gut	Prebiotic, anticancer, hypocholesterolemi c, agent, eco- friendly adhesive, and his thiskness in	(Ahmad et al., 2022)
	Lactobacillus reuteri FW-2		Phylum: Bacillota; Class: Bacilli; Order: Lactobacillales; Family: Lactobacillaceae	Sourdough	the food industry	(Taylan et al., 2019)
	Leuconostoc citreum BD170 7		Phylum: Bacillota; Class: Bacilli; Order: Lactobacillales; Family: Leuconostocaceae	Kefir grains		(Han et al., 2016)
Reuteran	<i>Lactobacillus reuteri</i> TMW1.6 56	$\begin{array}{ll} \alpha & -1,4 \\ linkage, & also \\ \alpha & -1,6 \\ glycosidic \\ bonds \end{array}$	Phylum: Bacillota; Class: Bacilli; Order: Lactobacillales; Family: Lactobacillaceae	Sourdough	Used in bakery	(Chen et al., 2016)
	Lactobacillus reuteri VIP		Phylum: Bacillota; Class: Bacilli; Order: Lactobacillales; Family: Lactobacillaceae	Culture collection of the Cereal Science laboratory of		(Sandra et al., 2012)

Table 1 Classification and application of various lactic acid bacteria producing different types of exopolysaccharides.

				University College Cork		
Kefiran	Lactobacillus kefiranofaciens subsp. kefirgran um BCRC 80410 ^T Lactobacillus kefiranofaciens JCM 6985 Lactobacillus delbrueckiisubs p. bulgaricus HP1	Presence of Glucose and galactose monomers form variable glycosidic bonds	Phylum: Bacillota; Class: Bacilli; Order: Lactobacillales; Family: Lactobacillaceae Phylum: Bacillota; Class: Bacilli; Order: Lactobacillales; Family: Lactobacillaceae Phylum: Bacillota; Class: Bacilli; Order: Lactobacillales; Family: Lactobacillales; Family: Lactobacillales;	Kefir grains Kefir grains Kefir grains	Enhances gut immunity, increases viscoelasticity of acid milk gels, has antibacterial and wound-healing qualities, lowers blood pressure and serum cholesterol, has the power to slow,tumour,growth , and can reduce blood pressure	(Wang et al., 2022) (Cheirsilp et al., 2018) (Frengova et al., 2002)
Inulin- type	Lactobacillus mulieris UMB7 800 Bifidobacterium longum IPLA E44	β-1,2 glycosidic bonds	Phylum: Bacillota; Class: Bacilli; Order: Lactobacillales;Family : Lactobacillaceae Phylum: Actinomycetota; Class: Actinomycetia; Order: Bifidobacteriales; Family: Bifidobacteriaceae	Female urinary tract Fecal sample	Prebiotics provide nutrition for gut mucosal cells while inhibiting pathogens . They can also be used as a replacement for fat in food products and for targeted medicine delivery to treat colon cancer.	(S. Zhang et al., 2023) (Salazar et al., 2009)
Oligosacc harides	Leuconostoc mesenteroides B 4 Pediococcus pentosaceus (SL001)	Aldose or ketose units are connected by glycosidic linkages in an iterative fashion.	Phylum: Bacillota; Class: Bacilli; Order: Lactobacillales; Family: Lactobacillaceae Phylum: Bacillota; Class: Bacilli; Order: Lactobacillales; Family: Lactobacillaceae	Intestines of largemouth bass <i>Micropterus</i> <i>salmoides</i> Home-made fermented anchovy sauce	Prebiotics, nutraceuticals, food additives, humectants, colon cancer prevention, chronic constipation treatment, lower blood lipid levels, and use in skin cosmetics	(Huang et al., 2023) (Hong et al., 2022)

i. Synthesis of HoPS

In the case of HoPS, they are synthesized by a sole enzyme which is encoded by only one gene. The enzyme glycosylhydrolase, known for its ability to cleave the glycosidic link of sucrose facilitates the coupling of glucosyl and fructosyl units, resulting in the formation of either α -glucans or β -fructans. Furthermore, it catalyzes the formation of HoPS (Figure. 2). The monosaccharide units are transferred to the polymer's reducing end using the energy supplied by the energetic glycosidic bond cleaving (Daba et al., 2021). Meanwhile, a membrane-associated glucosyltransferase produces α -glucans within the cell (Torino et al., 2015).



Fig. 2 Biosynthesis of Homopolysaccharides (GTF: Glucosyltransferase; FTF: Fructosyltransferase; Sucrose-derived monosaccharide).

ii. Synthesis of HePS

The synthesis of HePS comprises the following steps: During the initial step, the internalization of the sugar is carried out. During the breakdown of lactose, the Leloir route produces sugar nucleotides from glucose-6-phosphate, fructose-6-phosphate, or by utilizing glucose-1-phosphate. A membrane-bound polyphenyl-P sugar-1-P transferase called priming-GT catalyzes this step of the pathway. During the second step, sugar nucleotide precursors are produced from glucose-1-phosphate and fructose-6-phosphate, fueling the polymerization reaction. The membrane-bound GT facilitates the incorporation of sugar nucleotides into the process.

The third step consists of membrane transport via a flippase-mediated transport across the membrane. An enzyme known as flippase flips repeating units across the membrane (Wzx), which comprises 12 transmembrane domains. In the final step, polymerization occurs through diverse glycosyltransferase at the cytoplasmic membrane attaching the monosaccharide unit to the chains-reducing end (Jurášková et al., 2022). Numerous research studies have reported that optimizing the various physicochemical parameters can significantly boost the yield of EPS (Fig. 3. (A)).



Fig. 3 (A): Pathways for the synthesis of bacterial exopolysaccharides. (a) The Wzy-dependent pathway (A) (CM = cytoplasmic membrane; PG = peptidoglycan; GT = glycosyltransferase; P = phosphate).

Another pathway, through which the synthesis of microbial EPS occurs is the ATP-binding cassette (ABC)-Transporter dependent pathway (Fig. 3. (B)).



Fig. 3 (B): Pathways for the synthesis of bacterial exopolysaccharides: The ABC transporter-dependent pathway (B); (CM = cytoplasmic membrane; OM = outer membrane; PG = peptidoglycan; GT = glycosyltransferase; Und-P = undecaprenyl phosphate; P = phosphate; k = poly-2-keto-3-deoxyoctulosonic acid linker).

The primary function of this pathway lies in the synthesis of capsular EPS (CPS). The ABC-transporterdependent route produces CPS, which is assembled by glycosyltransferases (GTs) located on the inner membrane's cytoplasmic side. When only one operon containing GT is activated, this approach results in the synthesis of homopolymers, and when many GTs participate in the assembly process, it synthesizes heteropolymers (Fig. 3. (B)). Nevertheless, the export pathway through the interior membrane and its subsequent translocation to the cell surface differs. Facilitated by periplasmic proteins belonging to the families of polysaccharide co-polymerases (PCP) and outer membrane polysaccharide export (OPX), the ABC-transporters function as a bridge across the inner membrane. There is a linkage between these proteins and the PCP and OPX proteins that participate in the Wzx/Wzy pathways secretion mechanism.A tripartite efflux pump-like complex assists in the export of polymeric sugar chains across the inner membrane, allowing their migration to the cell surface. The synthesis of CPS in this pathway requires the assimilation of a conserved glycolipid, composed of a phosphatidylglycerol and a poly-2-keto-3-deocyoctulosonic acid linker at the reducing terminus, marking a pivotal distinction from the Wzx/Wzy and ABC-dependent pathways (Rana and Upadhyay, 2020). The key enzymes participating in the pathway may establish a comprehensive model of the metabolic flux which may help the researcher for generating flux balance analysis. Moreover, differential equations that depict the dynamics of EPS production over time can be created by applying Michaelis-Menten kinetics to the reactions that are catalyzed by important enzymes. Different scenarios can be simulated as well based on mathematical models that can help researchers find optimal production parameters. Nevertheless, incorporating scale-up effects, including shifts in nutrient dynamics and mixing processes, into models can support the transition from laboratory to industrial EPS production (Kleerebezem et al., 2002; Teusink and Smid, 2006).

5 Legal Recognition of EPS As A Novel Food Component

The European Food Safety Authority (EFSA) published the qualified presumption of safety list (QPS list) as a reference for supposed safety qualifications, which currently includes 39 LAB species and 5 Bifidobacteria species that are GRAS (EFSA Panel on Biological Hazards (BIOHAZ) et al., 2023). The EFSA and FDA have not endorsed health claims regarding using LAB-derived EPS in food items. When evaluating the safety of novel foods, EFSA will consider the following factors as needed: 1) The new food must be as safe as similar foods already available in the Union. 2) The innovative food's composition and usage rules must not pose a risk to human health in the Union. 3) A new food that is supposed to take the place of an existing food does not differ from the original food in such a way that consuming it frequently would make the consumer's nutrition poorer. The European Commission (EC) receives a novel food application from an applicant and confirms its legitimacy. Information about the food's composition, nutritional value, allergenicity, toxicological characteristics, manufacturing method, and intended uses must be provided by the applicant. Based on this information, the European Food Safety Authority (EFSA) evaluates the novel food's safety, considering variables such as absorption, metabolism, distribution, and excretion (ADME). EFSA provides a statement on the food's safety within six months. In the end, the EC determines whether to approve the novel food for the EU market and lays down any conditions for its usage (EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) Products et al., 2021). Although authorities approve certain LAB-derived EPS strains for use in food, adhering to EFSA regulations for novel food ingredients is a prerequisite to employing them as a purified ingredient in the European Union. Several other EPS have FDA approval and GRAS status, including bacterial cellulose, gellan gum, xanthan gum, Dextran, and curdlan (CFR - Code of Federal Regulations Title 21, n.d.). These EPSs are also listed as authorized in the Codex Alimentarius in the General Standard for Food Additives (GSFA Online Food Additive Index, n.d.) as well as by FSSAI in India as well (*Nutraceuticals_Regulations.Pdf*, n.d.).Since purified EPS is not used as food, it is considered a novel food additive and must therefore be authorized as safe for human consumption.

6 Applications of LAB-derived EPS in Different Sectors

EPSs demonstrate various functions such as texturizers, stabilizers, viscosifier, acting as biothickeners, or operating as emulsifiers, depending on the temperature, pH, and ionic strength of the medium (Abarquero et al., 2022).EPS improves the viscosity of solutions by establishing hydrogen bonds with water molecules, resulting in a three-dimensional network. This network traps water, causing a thicker consistency. They can stabilize emulsions by reducing the tension that exists between the phases of water and oil. The hydrophilic and hydrophobic portions of EPS molecules work together to form a stable interface, avoiding fat droplet coalescence and ensuring emulsion stability. Furthermore, by modifying the viscoelastic properties of food matrices, EPS can change texture features like creaminess or chewiness (Abarquero et al., 2022; Kavitake et al., 2020; Kumar et al., 2022). The change in pH can affect the charge and solubility of EPS, whilst temperature changes can change the viscosity and gelation properties, affecting EPS's usefulness in various formulations. Although, EPS possesses advantageous health properties such as antioxidant, immunomodulating, anticancer, antiviral, anti-cholesterolemic, and anticoagulant actions (Kang et al., 2022; Yildiz et al., 2023). Thus, based on the variety of applications that EPS offers, its addition to food products may offer health benefits to the consumers as well as sensory and morphological benefits to the food product.

6.1 Application in cereal and baking industry

The bakery industry uses hydrocolloids to enhance bread's machinability, texture, volume, rheology, and shelf life (Galle & Arendt, 2014). Therefore, boosting in-situ EPS generation by LAB during fermentation is recommended to improve bread's textural qualities, save expenses, and minimize the usage of extra chemicals. Moreover, studies have explored the inclusion of specific EPS-synthesizing LAB strains in sourdough as an innovative approach to address quality deficits in the functional characteristics of reduced-sugar products or to compensate for added fats in bread products (Sahin et al., 2019; Valerio et al., 2020). The beneficial benefits of EPS on bread are due to its ability to bind water and form networks with other ingredients in the dough. This can increase wheat bread's volume, rheology, and structure, which will improve the crumb's softness and reduce staling rates, giving it a longer shelf life (Korcz and Varga, 2021). Additionally, it has been noted that the incorporation of EPS-producing LAB has an anti-freeze effect and mitigates quality loss in frozen dough products (Jurášková et al., 2022). The inclusion of LAB strains such as Weissella cibaria L32 and Levilactobacillus brevis L17 in bread dough has played a crucial role in enhancing the quality of steamed bread fermentation. It led to an increase in titratable acidity and protease enzymatic activity during the fermentation process, as well as a significant improvement in the quality of steamed bread (Sha et al., 2023). In another report, the addition of Leuconostoc pseudomesenteroides DSM 20193 and Weissella cibaria DSM 15878 modified the physical properties of pea flour pastes (Shuai et al., 2023). LAB associated with cerealbased beverages synthesizes a vast variety of EPS due to the presence of glycansucrase activity, which elevates both the textural and organoleptic properties of the product (Werning et al., 2022).

6.2 Application in dairy industry

Despite the relatively small volumes of EPS produced by LAB, they play a crucial role in meeting consumer preferences for health-oriented additives in dairy products. EPS can reduce the need for added milk solids in dairy beverages, thereby addressing the demand for low-fat or fat-free options. They enhance mouthfeel and prevent syneresis while also improving the structure and texture of food products (De Vuyst et al., 2001). Furthermore, EPS interacts with proteins and micelles found in milk to make the case in network more rigid. The structure of EPS significantly influences its functionality. For instance, EPS derived from LAB exhibits

high inherent viscosities due to β -(1,4) linkages, leading to a consistent EPS solution (Torino et al., 2015). Negatively charged, low molecular weight EPSs may enhance immunological response, while neutral, high molecular weight EPSs have anti-inflammatory effects (Abarquero et al., 2022). Some EPS contains bioactive substances that may provide health advantages, such as prebiotic effects that promote gut health.

A study by Angelin and Kavitha (2020) reported that EPS produced by Leuconostoc and Pediococcus strains exhibited exceptional thermal stability, with melting temperatures exceeding 224°C, an important characteristic in dairy applications. Research on EPS-producing *Lacticaseibacillus paracasei* strains isolated from kefir demonstrated that the synthesized EPS increased milk viscosity at 20°C (223 mPa.s) and 30°C (217 mPa.s) compared to acid gels formed at 37°C (167 mPa.s)(Bengoa et al., 2023). The capsular and ropy EPS-producing strain *Streptococcus thermophilus* notably improved cheese quality by increasing moisture levels and enhancing the melting properties of mozzarella without negatively affecting whey viscosity(Petersen et al., 2000).Another example includes the development of quinoa-based yogurt fermented with the dextran-producing isolate *Weissella cibaria* MG1 (Zannini et al., 2018), showcasing the versatility of EPS in various dairy applications.

6.3 Applications in other sectors and novel approaches

EPSs are used widely in the cosmetic industry as a moisturizer owing to their excellent water retention capacity in the preparation of creams and lotions (Waoo et al., 2023). Pullulan is stable at very high temperatures along with its stability at different pHs and most metal ions owe to its number of applications in cosmetic creams, lotions, and shampoos (Singh et al., 2023). Levan is utilized in whiteners, food packaging films, and cosmetics in the formulation of hair care products. It has been noted that Leuconostoc, Streptococcus, and Lactobacillus (particularly Lactobacillus gasseri) contain inulosucrase, proving their capacity to produce inulin and levan (Anwar et al., 2010). In the cosmetic industry, dextran is used as a binding agent that enhances the components' dispersion in cosmetic formulations. A famous dextran-producing strain of LAB is Leuconostoc mesenteroides NRRL B-512F which is widely used at industrial scale (Zikmanis et al., 2020). Apart from this EPSs are highly capable of forming hydrogels and retaining significant levels of water encapsulated in their cross-linked 3D network structures while maintaining insolubility, making them interesting candidates for use as intelligent drug micro and nano-carriers. The nanoscale scale can impart distinct physicochemical features to EPS, and these constructs can communicate with the cells and tissues at a molecular level (Morais et al., 2022). These nanogels possess a hydrophobic core capable of entrapping hydrophobic drugs, making them a prospective carrier for drug delivery owing to the sustained size stability of the polysaccharides. EPSs have a remarkable capacity to absorb and hold water, creating a matrix that resembles gel. This hydrophilic property keeps a moist environment that can aid in drug release in addition to supporting the encapsulation of medicinal substances. It was reported by Charoenwongpaiboon et al. (2021) that the EPS isolated from Leuconostoc holzapfelii KM01 could form the hydrogen or nanoparticle depending on their concentration as well as was non-toxic which significantly increased the solubility of quercetin. EPS from LAB typically exhibit low cytotoxicity and fewer side effects, making them a favorable alternative to synthetic anti-tumor agents. The EPS from Weissella paramesenteroides MN2C2 had significant anti-tumor activity against Liver HepG-2, Colon CaCO-2, and Breast MCF-7 malignant cells (Amer et al., 2021). EPS can alter the immune system, whether it be an innate or adaptive response, and thus acts as an immunomodulator. LAB-based EPS is also known recently to be used for the development of ointments applicable in the healing of cutaneous wounds (Abdel-Monem et al., 2022). LAB-based EPS is also used for controlled flavor release in different types of food products (Koh et al., 2024). In a study, Pediococcus acicilactici S1 had a considerable effect on the gelation characteristics and microstructure of porcine myofibrillar protein, which can be further exploited to build coatings and films(Lu et al., 2024). The EPS produced by Enterococcus faecium PCH.25

isolated from cow butter exhibited novel antilisterial activity and could be used for the treatment of *Listeria monocytogenes* (Chegini et al., 2024). Various commercial applications of EPS isolated from LAB can be explored by studying the molecular dynamics and kinetics of the production of EPS by LAB and what factors govern them. Mathematical modeling could improve EPS features for targeted medication administration by simulating and forecasting their behavior under various conditions. This approach enables researchers to examine parameters such as drug release rates and diffusion mechanisms, assisting in the identification of ideal EPS compositions for increased encapsulation efficiency and targeted release, ultimately increasing therapeutic efficacy.

7 Role of Mathematical Modeling In Microbiology

Mathematical modeling can be defined as converting a real-life situation into mathematical expressions, commonly by constructing equations, and then employing this mathematical expression to gain more profound insight into the initial problem and discover novel aspects of the subject matter. The purpose of each equation is to characterize relationships within the model, derived from the observed behavior of the natural phenomena. Any changes in the latter should manifest in the mathematical model's behavior. A good model should always reveal the common characteristics or attributes it aims to reproduce. In biological systems, mathematical models are synthetic. For instance, there are communities of microorganisms that are regenerated from pure cultures. Regardless of how complicated the combination is the model can never fully replicate the natural system due to the difficulty of substantiating the absence of an unidentified, unculturable organism that potentially influences the natural community. Due to their extreme complexity, actual systems have to be replaced by imaginary systems which can be controlled mathematically. However, the validity of the assumptions will determine the application of the results to the biological system. The construction of such models gives a systematic means of understanding the behavior of specific systems for which experimental data is available. This technique motivates the microbiologist to be precise in his assertions and definitions. Terms such as growth yield, oxygen uptake, and so on must be represented mathematically to avoid ambiguity (Topiwala, 1973). Realistic and validated models serve as important guidelines for the design and operation of industrial microbiological processes. Mathematical modeling predicts behavior in untested situations or tests the plausibility of various proposed causes. This strategy frequently identifies a key region where additional trials should be conducted. According to the most accepted plan outlined by Whiting and Buchanan (1993) regarding the classification of mathematical models, they fall into three categories: primary, secondary, and tertiary models. In terms of mathematical modeling, the primary models are those mathematical equations that can describe the inactivation of microbes, survival rate, or growth rate by considering cell population and cell density over time within specific environmental and cultural conditions. Primary models could be used to describe EPS production by specific LAB strains under different growth conditions. The core purpose of such mathematical models is to evaluate the model's capability to align with individual growth curves and perform parameter estimation. Secondary models are employed to articulate how primary models react to environmental factors such as temperature and pH. To forecast survival or growth curves, environmental characteristics are used in conjunction with primary and secondary models. The secondary models can be used to indicate complex behaviors that include numerous variables. They can examine the impact of different formulation parameters in this context. The overall model is then scrutinized, and commonly applied within the domains of predictive microbiology. Through the combination of one or more primary and secondary models, tertiary models provide a reliable system for predicting the behavior of individual microbes in changing situations. These models are often incorporated into predictive microbiology software, designed for accessibility by individuals without modeling expertise(Li et al., 2007). Tertiary models can be used to

anticipate how LAB-EPSs react in biological contexts, accounting for aspects like cellular interactions and degradation kinetics. While building a model for a microbiological complex system, only those parameters that are relevant to the objective should be considered. The knowledge of the microorganisms and their interaction with their environment is crucial when setting a hypothesis that will be further used to interpret the data. The variables chosen for the model used for a microbiological system cover criteria such as microbial growth, production of metabolites, and population death rates. The utilization of differential equations proves instrumental in capturing the intricacies of the macroscopic domain. Consequently, the principles of diffusion outlined by Fick, Navier-Stokes equations, and Schrödinger equations are dependable and aptly describe phenomena in the macro world, often referred to as continuous models. In the microscopic realm, we shift away from managing a set of interlinked processes. In this context, an effective strategy is discrete modeling where time, space, and state can remain discrete. Equation-free models are also gaining popularity as a means to address the increasing influx of data and knowledge (DeAngelis and Yurek, 2015; Ye et al., 2015). Modeling is critical for LAB-EPS applications because it predicts behavior, optimizes production processes and characterizes attributes. It evaluates biocompatibility, facilitates scaling up production, and allows formulation design through predictive analytics. In general, modeling improves the creation and use of LAB-EPSs in the biotechnology, food, and pharmaceutical industries. Throughout the years, there has been ongoing development of tools to qualify and quantify microbe-driven systems, enabling theorists to refine their ideas with the possibility of better engineering the structure and operation of biological systems. Moreover, the idea of individual strains or indiscriminate biomass has historically given way in microbiology to the idea of microbial ecosystems with several species, adding an ecological component that has expanded the possibilities for mathematical modeling to include both individual and community-based methods. Apart from suspended growth systems, researchers have focused on models for attached or fixed growth in a variety of industries, including healthcare and medicine, water treatment systems, and other parts of microbial ecology.

8 Role of Modeling in Process Design Construction and Control Of The Design in LAB Research

The implementation of process control in biotechnology involves the application of different models, such as adjusting various process parameters during fermentation based on an online assessment of fermentation metrics. This model encompasses a broad range of phenomenological equations, encompassing the microbial growth-regulating Monod and Pirt equations as well as opaque models like artificial neural networks (ANN). These components play a crucial role in connecting process measurements with fermentation properties (Teusink and Smid, 2006). Various models contribute to food microbiology, especially in the context of food safety, where predicting the growth pattern of pathogens is important. Some of the mathematical models used in LAB research have been reported by different authors (Table 2).

Bacterial source	Mathematical model used	Equation	Findings	Reference
Leuconostoc lactis, Lactococcus lactis subsp lactis and Lactiplantibacillus plantarum	Power law model	$T = \kappa \gamma^{n} \text{ where,}$ T = shear stress, $\kappa = \text{Consistency}$ index, $\gamma = \text{shear}$ rate and n = flow index	Consistency index (κ) values ranged from 0.02 – 320.67 for 0.2% (w/v) concentration; 42.98 – 40000.26, 0.35 – 402823.27, 0.06 – 6059.23 for concentrations 0.4%, 0.6%, 0.8% and 1.0%, the consistency index values ranged from 0.00 to 14953.67, while the flow index (n) exhibited shear- thinning characteristics with values ranging from 0.03 to 3.13 for 0.2% 0.06 to 0.82 for 0.4%, 0.38 to 1.85 for 0.6%, 0.14 to 2.26 for 0.8% and	(Adamu- Governor et al., 2023; Daud et al., 2023)
Lactobacillus plantarum, Lactobacillus acidophilus and Lactobacillus rhamnosus	Gompertz model	$y=ae-e^{b-cz}$ where, <i>a</i> , <i>b</i> , <i>c</i> = model equation coefficients <i>x</i> = incubation time (h) <i>y</i> = changes in electrical impedance of the growth medium (%).	Applying the Gompertz model allowed us to ascertain the parameters governing the dynamic shifts in the electrical impedance of the substrate. Which was as follows: $Z_b = \int_0^{24} f(x) dx$ I_{max} =maximum rate of change of electrical impedance $I_{max} = (a^*c)/e$ e = 2.7183 x_I =achievement time of I_{max} Z_b =potential of bioconversion.	(Biadała et al., 2023)
Enterococcusdurans K48, Enterococcus faecium R114, and Enterococcus faecium T52	Quadratic model (Response surface methodology)	$\begin{split} \mathbf{Y} &= \boldsymbol{\beta}_0 + \sum \mathbf{i}^{\ \mathbf{k}} \boldsymbol{\beta}_i \\ \mathbf{X}_i + \sum_i^{\ \mathbf{k}} \boldsymbol{\beta}_{ii} \mathbf{X}_i^2 \\ &+ \sum_i^{\ \mathbf{k}} \sum_j^{\ \mathbf{k}} \boldsymbol{\beta}_{ij} \mathbf{X}_i \\ \text{where,} \qquad \mathbf{Y} = \\ \text{response,} \boldsymbol{\beta} 0 = \\ \text{constant} \text{value} \\ \text{Y-intercept,} \\ \boldsymbol{\beta} i = \text{constant} \text{value} \\ \text{Y-intercept,} \\ \boldsymbol{\beta} i = \text{constant} \text{factor of the first} \\ \text{order,} \boldsymbol{\beta} i i = \\ \text{constant} \text{factor} \text{of the second} \\ \text{order,} \boldsymbol{\beta} i j = \\ \text{constant} \text{factor} \\ \text{of the second} \\ \text{order,} \boldsymbol{\beta} i j = \\ \text{constant} \text{factor} \\ \text{of interference} \\ \text{parameters,} \text{Xi} \\ \text{and} \text{Xj} = \text{the} \\ \text{values} \text{of the} \\ \text{factors} i \ \text{and} j \\ \text{respectively} \end{split}$	The optimization plots exhibited the highest EPS yield for <i>E. durans</i> K48, <i>E. faecium</i> R114, and <i>E. faecium</i> T52 occurring at 38.4, 37.4, and 36.7 °C and pH of 5.9, 5.6, and 5.8, respectively, cultured in a Sucrose-MRS medium which was in accordance with the predicted value by the model	(Rahnama Vosough et al., 2022)
Lactiplantibacillus plantarum 60-1	Luedeking–Piret	$\mathbf{r}_{P} = (\alpha r_{X} + \beta X)$ Where $\mathbf{r}_{P} =$	No product inhibition was observed Both glucose	(Vera-Peña et al 2022)

Table. 2 Various mathematical	models used in LAB research.

		volumetric rate of lactic acid production, α = growth associated product constant and β = no growth associated product constant.	and lactose were metabolized in a concomitant manner.The consumption of glucose and lactose was concomitant, with 99.75% glucose and 91.16% lactose consumed at the end of fermentation.		
Lactiplantibacillus plantarumLS5and LU5	Elovich model		The mathematical model using a genetic algorithm exhibited that the most significant EPS production occurred with LS5, especially at 50% amplitude.	(Bagher Hashemi al., 2022)	et
Lactobacillus plantarum (NR_104573.1) and Pediococcus pentosaceus (NR_042058.1)	Ritger–Peppas kinetics model	$M_t/M_0 = Kt^n$ where, Mt /M0= the ratio of active ingredient kinetics at time t and n; K= constant;	The Ritger–Peppas kinetics model was the most appropriate model for the data, as it had the maximum regression correlation value for encapsulated <i>L.</i> <i>plantarum</i> and <i>P.</i> <i>pentosaceus</i> both with and without EPS, which suggested that the model accurately represented a swellable system.	(Abedfar al., 2021)	et
Leuconostoc pseudomesenteroides JF17	Luedeking-Piret model	$\frac{\mathbf{d}_{\mathbf{p}}/\mathbf{d}_{t}}{\mathbf{d}_{x}/\mathbf{d}_{t} + \boldsymbol{\beta}\mathbf{x}}$ where, α and β = product formation constants; $\mathbf{d}_{\mathbf{p}}/\mathbf{d}_{t}$ = product formation rate	The model revealed that the JF17 strain's EPS synthesis appeared to be connected with the microorganism's cell proliferation.Furthermore, it exhibits high efficiency in producing the EPS from a substrate, with a yield of 17.85 ± 0.74 mg EPS per log CFU (Yp/s).	(Farinazzo al., 2022)	et

Models optimize EPS generation efficiency by dynamically modifying process parameters in response to online fermentation metrics. They offer predictive insights into microbial growth and EPS yield, allowing for more effective planning and resource allocation. Effective modeling also aids in the detection of quality issues early in the manufacturing process, maintaining consistent EPS quality and reducing waste. Models also help with the design of fully automated manufacturing processes, which streamlines production and reduces human error. Modeling enables the identification of ideal circumstances by simulating numerous scenarios, resulting in reduced development time and costs. Throughout the production process, food safety can be upheld by forecasting potential contaminants' growth patterns utilizing modeling in the field of food microbiology. Finally, a balanced approach that includes mathematical and empirical validation ensures that models adequately reflect the bioprocesses involved, allowing for dependable production implementation. Overall, modeling is important in improving the efficiency, safety, and quality of LAB EPS manufacturing (Ates, 2015;

Ferrer Valenzuela et al., 2015; Teusink and Smid, 2006). A significant number of models have been developed recently that are uniquely tailored to LAB and their metabolites (Galgano et al., 2023; Patel et al., 2023; Teusink and Smid, 2006). These models developed specifically for LAB can be significantly used in process design and control. The criteria that are taken into consideration when developing a model are explained in Figure 4.A model's validity should not be determined solely by mathematical rationality, nor should it be determined solely by empirical validation at the expense of mathematical and scientific principles (Avula, 2003).



In the validation process, a combination of rationality and empiricism (logic and pragmatism) should be applied. If necessary, all or some of the processes in the modeling process should be performed numerous times until the model proves appropriate for implementation (Avula, 2003).



Fig. 5 Role of mathematical modeling in process design and control.

The role of mathematical modeling in process design and control is very vital and has been explained in Fig. 5 concerning the pros of its application and cons of not applying it in statistical experimental data. The developed model illustrates the bioprocesses that successfully result in the formation of fully automated manufacturing steps. In addition, because two processes were regulated online and quality-related aberrations were detected early, effective data logging, modeling, and process management were critical for quality. Finally, by merging modeling and simulation, we were able to significantly minimize development time and expense.

8.1 White box models

White box models can be defined as those models where all pertinent mechanistic information is incorporated to calculate functional performance based on system parameters representing features of real objects or processes. They are applied when the input, output, and internal dynamics of the system are known (Habash, 2022). The researcher must have all the information about the system to derive a white-box model. Mechanistic systems, electric circuits, and intercellular kinetics can be studied by using white-box models as they can be understood well in terms of mechanistic models. White-box models can be used for the identification of the possible factors slowing down the metabolic process in the industry during the product development phase (Teusink and Smid, 2006). The white-box technique encompasses various families of algorithms, of which we shall discuss the most commonly used ones in the literature. These include decision trees, rule-based systems, and fuzzy patterns. Based on graph theory, a decision tree (DT) combines decision support system components with tree structure components. A directed graph has precisely one path connecting any two vertices. Models with a rule foundation are regarded to be understandable models. An expression that describes a group of things is called a rule. A rule is typically stated as an IF-THEN logic inference with relational statements as the antecedent and labels as the consequent. In the case of rule-based systems, they are widely used in practical situations, including software defect prediction, inferring causal gene regulatory networks, and analyzing currency portfolio efficiency. Similar to a rule-based approach but without the consequence, Dong and Li proposed the contrast pattern-based model in the late 1990s. A pattern is a language-specific statement that describes a set of objects. A pattern is typically expressed as the conjunction of relational assertions (also known as items), each having the following form: [fi # vj], where # is a relational operator from the set $\{\in, \notin, =, \neq, \leq, >\}$ and vi is a value in the domain of feature fi. A novel pattern type known as fuzzy patterns was created by employing fuzzy sets to improve contrast patterns. Compared to contrast patterns, these patterns show a vocabulary that is closer to that of human specialists. The elements of a fuzzy pattern are selectors [Feature \in FuzzySet], where \in denotes that the value of the feature is a member of FuzzySet. Because of this, an object can be said to partially satisfy a pattern depending on how well its feature values match the pattern's item description. White box models are useful tools for utilizing LAB to produce EPS in the lab. Through the application of their profound knowledge of metabolic pathways and mechanisms involved in EPS biosynthesis, researchers generate accurate simulations of the EPS synthesis mechanism. These models can accurately forecast how various variables affect EPS yield by incorporating mechanistic information, such as the functions of certain enzymes and the impact of environmental parameters (such as pH and temperature). These models can locate regions that restrict the total amount of EPS synthesized, by identifying bottlenecks in the biosynthesis process. Using the Gompertz model, the bacterialisolate Lactobacillus delbrueckiisubsp. bulgaricus 2214 was subjected to evaluation for the production of EPS at different stages, such as the study of the *epsE* gene expression, quantification of the dry weight of EPS, and attaining the ultrastructural characterization of the EPS so that the fit of the model can be confirmed. The positive value of $\Delta E\%$ with the EPS production suggests that the model fits well (Bancalari et al., 2019). With this knowledge, researchers can optimize process parameters and develop more productive production techniques(Goodswen et al., 2021; Roupas, 2008; Taiwo et al., 2024; Teusink & Smid, 2006). The application of white-box models can help researchers and industries overcome the loss of product and optimize the parameters more appropriately to get better results.

8.2 Stoichiometric models

In contrast to other biological systems, metabolic networks enjoy a higher level of understanding. The rationale behind this is comprehensive knowledge of both the metabolites in the biological system and the reactions that interconnect and convert the various constituents of metabolism. In computational systems biology, there is a widespread application of stoichiometric models for the quantitative analysis of metabolic networks (Kulyashov et al., 2023). They quantify intracellular mass flow at a steady state, i.e., they assume stationary systems and depict basic cellular biochemistry in metabolic networks. The process of characterizing stoichiometric models entails encapsulating them in a stoichiometric matrix, which clarifies the role of metabolites in every reaction. The entries show stoichiometric coefficients, and the reactions are presented as columns with the metabolites in rows (Teusink and Smid, 2006). In the case of estimation of metabolic flux, a stoichiometric model is constructed which contains an array of various reactions that convert nutrients present in the system into biomass and residual products (Antoniewicz, 2021). Under the assumption of a (quasi) stable state for internal metabolites, developing a set of mass-balance equations for these metabolites becomes possible. Establishing equations for the mass conservation of metabolites is the first stage in the modelbuilding process. Our poor understanding of the system leads us to believe that metabolite concentrations vary over time, requiring the modeling of these dynamics with ordinary differential equations. By resolving these equations, a relationship between the measured fluxes and all other fluxes is established, making it possible to compute the latter (Teusink and Smid, 2006). Stoichiometric models are extremely useful in researching EPS manufacturing for a variety of reasons. They allow researchers to monitor the conversion of available nutrients like as carbon, nitrogen, and phosphorus into biomass and EPS, which is critical for maximizing EPS yields.In stoichiometric analysis for EPS synthesis, two essential yield coefficients are important: Y_X/S (Biomass Yield Coefficient) and Y_EPS/S (EPS Yield Coefficient). Higher values indicate a more efficient conversion of substrate into cells. Y_X/S is a measure of biomass generated per unit of substrate consumed. In contrast, Y_EPS/S represents the amount of extracellular polymeric substances produced per unit of substrate eaten, with larger values indicating greater EPS production efficiency. These coefficients, when combined, allow researchers to analyze the efficiency of EPS generation to nutrient intake and lead optimization tactics in a variety of industrial applications. Establishing mass balance equations to depict the conversion processes is the fundamental step in stoichiometric models. The following could be the format of a typical mass balance for a microbial culture:

$$S_0 - S_f = Y_{X/S} \cdot X + Y_{EPS/S} \cdot EPS$$

where: S_0 is defined as the initial substrate concentration; S_f is defined as the final substrate concentration; X is defined as the biomass concentration; EPS is the concentration of EPS produced; $Y_{X/S}$ and $Y_{EPS/S}$ are the respective yield coefficients.

This approach is useful because it enables the quantification of internal flux distributions that are typically hard to measure. For instance, consider two parallel pathways with identical end products. Simply measuring the end product of both reactions doesn't offer insights into the internal flow distribution between these parallel pathways. Yet, when labeled substrates are incorporated the subsequent measurements of labeled intermediates in both pathways occur which enables the measurement of relative metabolic fluxes between the two pathways. Metabolic flux analysis techniques have become a well-known methodology widely used for

various industrial applications such as industrial fermentation procedures, and amino acid production as well as in various other applications (De Falco et al., 2022). Apart from metabolic flux models, the elementary flux models have proven very useful in the case of metabolic engineering studies. An elementary flux model is delineated as the smallest group of enzymes capable of operating under stable conditions(Said et al., 2023). Any constant-state flux distribution can be represented as a nonnegative linear combination of elementary flux modes. Qiu et al. discovered a proteome trade-off between *Lactobacillus plantarum* HMX2's primary metabolism and EPS generation, which was subsequently mechanistically represented by a regulatory proteome-constrained flux balance analysis (RPCFBA) model. The model satisfactorily captured the growth rates as well as the EPS production fluxes that were induced by acid stress. Moreover, the greatest yielding flux model inherently includes both the maximum theoretical yield and the technique to reach it, because the paths are elementary and non-decomposable. As the need for bioproducts develops, insights from stoichiometric models will aid in our knowledge of microbial metabolism and the optimization of fermentation techniques for long-term EPS production.

8.3 Kinetic models

Kinetic models can be termed mechanistic representations of biological systems in the case of mathematical modeling in biological aspects (Maeda and Kurata, 2023). A kinetic model consists of information in two main categories. The first level consists of metabolites produced by the cell, various signaling molecules that are used by the cell as well as chemical reactions that are involved in the model with that of the formulations that are employed in reaction kinetics such as the Michaelis-Menten kinetics. The secondary category of the information consists of all the information that is related to numerical values assigned to parameters within the primary information category (Hasdemir et al., 2014). When stoichiometric models are applied, it is possible to identify a flux or pathway that, when enhanced leads to an increased product yield. A key challenge, however, is determining how to effectively increase this flow. Thus, in answer to this query, we have to apply kinetic models. In the reaction, the enzyme kinetics, guide the alteration of parameters required to achieve a specific change in the system. Various specific kinetic models have been devised for metabolic pathways. Kinetic models aid in the delineation of metabolic pathways involved in EPS generation using metabolic flux analysis (MFA), revealing critical pathways and substrate constraints that affect EPS yields. Models such as the Luedeking-Piret model allow researchers to study fluctuations between the exponential and stationary phases and optimize settings for each type of EPS generation. These models discriminate between growth-associated and non-growth-associated EPS production. Furthermore, kinetic models make it easier to estimate crucial characteristics like yield coefficients and the maximum specific growth rate, which helps to analyze production efficiency. They enable simulation of how environmental parameters such as temperature, pH, and nutrient availability affect EPS production, assisting in the identification of ideal conditions for improved synthesis. Dynamic modifications during fermentation are made possible by integrating kinetic models with real-time monitoring, and feedback control systems automate interventions based on predictions from the models. The application of the Luedeking-Piret model proposed that the EPS generation by the Leuconostoc pseudomesenteroides JF17 strain seemed to be connected with microorganism cell development, alongside its high efficiency in producing the polysaccharide from the substrate ($Y_{p/s}$ ¹/₄ 17.85 ± 0.74 mg EPS/log CFU) (Farinazzo et al., 2020). The Luedeking-Piret model distinguishes between two key components of product formation i.e., Growth-associated production which is directly related to bacterial growth, and Non-growthassociated production which happens outside of growth, frequently during periods when growth is halted or slowed down. The mathematical expression for the Luedeking-Piret model is:

$$\frac{dP}{dt} = \propto \frac{dX}{dt} + \beta X$$

Where α represents growth-associated EPS production; β represents non-growth-associated EPS production; dP/dt is the rate of EPS formation; dX/dt is the rate of LAB growth and X is the concentration of biomass (Petersen and Amstutz, 2008).

During the exponential growth phase, most EPS is produced concurrently with biomass expansion (growth-associated), however in the stationary phase, EPS production continues even after growth slows (nongrowth-associated). By fitting experimental data into the model, researchers can learn how different stages of bacterial growth affect EPS generation. The kinetics of Streptococcus thermophilus LY03 fermentation parameters were the outcome of a kinetic mathematical model that describes the development, EPS production, and degradation by S. thermophilus LY03 (Roupas, 2008). The model suggests that the initial complex nitrogen concentration has a profound effect on EPS production kinetics. The specific EPS production is influenced by the C/N ratio, causing a doubling of Kf(Specific EPS formation) with higher initial complex nitrogen concentrations (Degeest and De Vuyst, 1999). Similarly, in another study, an EPS production kinetic study was done on Lactiplantibacillus plantarum LS5 and LU5. The maximum EPS output at various amplitudes was reported with LS5 and a 50% amplitude. Across different amplitudes, the Elovich model predicted constants were close to the average values, affirming its efficacy in delineating the kinetics of EPS generation (Bagher Hashemi et al., 2022). The implementation of simplified kinetics in biology has the potential to greatly widen the variety of kinetic models that can be efficiently handled. Overall, kinetic models offer a comprehensive framework for improving EPS production, hence increasing efficiency and productivity in both research and industrial settings.

8.4 Global metabolic models

In today's technological era, high-throughput data is available. With the increase in the amount of this vast amount of data, multivariate analysis of the data has become very popular in systems biology. These techniques are nowadays been used extensively for metabolomic, transcriptomic, and proteomic data. In this instance, an alternative strategy to leverage this data and integrate vast genomic-scale information is through the construction of genomic-scale metabolic models. Bioinformatic techniques are used to search the genome for open reading frames that code for proteins having enzymatic activity. The presence of such genes, along with current biochemical and physiological data, can be utilized to predict probable metabolic pathways (Prosser et al., 2014). The main elements in the production of a genomic-scale model are, initially, identifying and closing gaps which means those reactions in the network of the pathways that should be indicative of presence based on biochemical and physiological evidence, but no identifiable gene is found in the genome (Osterman, 2003). The second step is to ascertain how cofactors are used in processes. One key example is whether NAD, NADP, or both are employed as electron acceptors. Third, it's necessary to quantify the energy coefficients associated with growth and maintenance. Fourth, the organism's biomass composition, ideally under the necessary physiological parameters, should be comprehended. Once a metabolic model at the genome scale is set up, a wide range of investigations can be performed to investigate the model's metabolic capabilities (Teusink and Smid, 2006). The objective of flux balance analysis is to obtain the optimal value for a predetermined goal such as biomass production and yield by optimizing the flux distribution within the metabolic network. Constraint-driven modeling methodologies utilize comparable, if not identical, methods as those applied in the traditional material flow analysis such as metabolic balancing and linear programming. In contrast to analyzing extensive transcription ratios, one might assert that the expedited generation of hypotheses occurs when microarray data is visualized on metabolic maps. As a result, global metabolic models contribute to both the inductive and deductive aspects of scientific thinking. Precursors from various locations in metabolism are required simultaneously for the synthesis of complex compounds such as heterologous proteins and EPSs. Excessive product production can disrupt metabolic flux distributions and negatively impact engineered strain performance. Flux balance analysis can be used in genome-scale models to forecast imbalances between input and output, or between the medium's composition and the products produced. Additionally, these imbalances can be monitored and incorporated using global read-out techniques such as transcriptomics or metabolomics. Stoichiometric and energetic investigations provide insights into the energy and precursor demands for EPS synthesis, leading to tailored interventions. Additionally, the model permits gene knockout simulations, identifying critical genes for increased EPS generation that may be verified through experimentation (Teusink and Smid, 2006; C. Xu et al., 2013).In a recent investigation, a ground-breaking genome-scale metabolic model for *Lacticaseibacillus casei* was developed, encompassing 846 genes, 969 metabolic processes, and 785 metabolites. The model's construction involved a dual approach, utilizing both manual genome annotation and an automatic SEED model. The validation of the iJL846 model was carried out by simulating cell growth on 15 recognized carbon sources (N. Xu et al., 2015). Thus, by integrating predictive capabilities with experimental validation, global metabolic models considerably speed up the process of optimizing EPS generation in microbial systems.

9 Contribution of Mathematical Modelling in EPS Production

Numerous investigations have focused on developing and improving models that faithfully capture the complex relationships among microbial metabolism, growth dynamics, and EPS generation. Researchers used several modeling methodologies to better understand the physiological and metabolic processes driving EPS formation, from basic kinetic models to more advanced computational simulations. These models have been quite useful in identifying crucial elements that influence EPS yield, such as nutrient availability, ambient conditions, and fermentation parameters. By employing an artificial neural network model, researchers found that *Pediococcus pentosaceus* enhanced its exopolysaccharide output by 32.5%, from 1.83 ± 0.01 g/L to $2.35 \pm$ 0.02 g/L(Yang et al., 2024). The study provided a potential method to monitor the precise prediction of the fermented products synthesized in real-time. The yield of EPS can also be altered using the provision of external treatment which may lead to a higher yield of EPS. Apart from the general physicochemical parameters, the effect of such treatments can also be predicted by using mathematical modeling. Hashemi et. al.(2022) using the Elovich model (EM) produced the α and β values (EPS production constant), which showed that LS5 had the maximum EPS production with an amplitude of 50%. The model predicted that applying sonication at 100 W, 30 kHz, and 50% amplitude for 15 minutes is a suitable choice when producing EPSs on a big scale. Recent genome sequencing studies have revealed entire genome data for a variety of species, enabling researchers to gain a deeper comprehension of biological processes including cellular metabolism and signal transmission. As a result, genome-scale metabolic models have been created, which can be produced rapidly utilizing software tools that use the genetic, biochemical, and physiological data of an organism. These models are critical for high-throughput data integration, metabolic engineering strategy development, process optimization, and real-time control (Ates, 2015). Metabolic models aim to enhance fermentation byproduct production and investigate metabolic processes in the food and nutrition industries. A dextran type EPS producing LAB L. pseudomesenteroides JF17, on analysis of its production kinetics using Luedeking-Piret model suggested that the JF17 strain was highly efficient at producing the polysaccharide from the substrate (Yp/s = 17.85 ± 0.74 mg EPS/log CFU), and its EPS production seemed to be linked to the microorganism's cell development (Farinazzo et al., 2022). Similarly, another type of mathematical model called the Voight function was used to optimize the physicochemical parameters for EPS production by Lactiplantibacillus plantarum YT013. After the analysis using the Voight function, it was noticed that the EPS synthesis initially increased and subsequently stabilized over time. This observation showed that the Voigt nonlinear model fits the data well, as it was in line with the ideal outcomes (Zhang et al., 2023). Various other studies with their findings have been discussed already in Table 2 as well separately in sub-sections of section 8based on the mathematical model used. Mathematical models play an important role in exopolysaccharide industrial production because they provide a systematic method for optimizing numerous physicochemical characteristics. In addition to facilitating a better comprehension of the fundamental biochemical processes, these models also make it easier to design fermentation systems effectively, which raises yields and lowers production costs. Implementation of these models can fine-tune the manufacturing process, providing improved quality and consistency in the end product, thus enhancing both the scalability and sustainability of EPS production in industrial settings.

10 Conclusion

Mathematical modeling in LAB-synthesized-EPS research has proven beneficial in understanding and optimizing EPS synthesis by simulating biological, biochemical, and environmental interactions that affect the process. Models assist in predicting how changing conditions affect EPS yields and quality by incorporating a variety of parameters, including genetic regulation and nutrient availability. This systematic approach to experimental design and scaling is beneficial for industrial applications. Prospectively, modeling developments will probably concentrate on integrating multi-omics data-genomics, proteomics, and metabolomics, for example—into stronger models. Furthermore, these models will be refined with the use of machine learning (ML) and artificial intelligence (AI), enabling increased adaptability to dynamic settings and real-time industrial processes. Hybrid models that combine mechanistic and data-driven approaches will increase prediction flexibility and accuracy. The prospective effects of these advances in mathematical modeling on a variety of businesses are noteworthy. Increased production of EPS in the food sector may improve the stability and texture of fermented foods like cheese and yogurt, as well as the efficacy of probiotics. In the pharmaceutical and biomedical disciplines, EPS has interesting applications, such as immunomodulatory and anticancer capabilities, and mathematical models can help optimize manufacturing for specific therapeutic applications. Improved LAB-EPS production can also be advantageous for agricultural and environmental applications such as bioremediation, soil conditioning, and plant growth encouragement. Overall, mathematical modeling will remain critical in improving LAB-EPS research, driving EPS production advancements, and aiding the discovery of novel strains and conditions with the potential to revolutionize applications across multiple industries. Further comprehensive research on mathematical models for EPS derived from LAB, along with insights into their systematics and metabolic pathway kinetics should be done. Given the versatile nature of bacterial EPS, their utilization is poised to skyrocket across various industries in the years to come.

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