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Review

Microbial Interactions within the Cheese Ecosystem and Their Application to Improve Quality and Safety

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Abstract: The cheese microbiota comprises a consortium of prokaryotic, eukaryotic and viral populations, among which lactic acid bacteria (LAB) are majority components with a prominent role during manufacturing and ripening. The assortment, numbers and proportions of LAB and other microbial biotypes making up the microbiota of cheese are affected by a range of biotic and abiotic factors. Cooperative and competitive interactions between distinct members of the microbiota may occur, with rheological, organoleptic and safety implications for ripened cheese. However, the mechanistic details of these interactions, and their functional consequences, are largely unknown. Acquiring such knowledge is important if we are to predict when fermentations will be successful and understand the causes of technological failures. The experimental use of "synthetic" microbial communities might help throw light on the dynamics of different cheese microbiota components and the interplay between them. Although synthetic communities cannot reproduce entirely the natural microbial diversity in cheese, they could help reveal basic principles governing the interactions between microbial types and perhaps allow multi-species microbial communities to be developed as functional starters. By occupying the whole ecosystem taxonomically and functionally, microbiota-based cultures might be expected to be more resilient and efficient than conventional starters in the development of unique sensorial properties.

Keywords: cheese; cheese microbiota; lactic acid bacteria; starters; adjunct cultures; cheese quality; cheese safety; high throughput sequencing; microbial interactions; community assembly

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1. General Introduction

Cheese is a fermented milk product that dates back to Neolithic times. Traditionally, cheese was a milk-derived food that served as a means of preserving milk and its remarkable nutritive properties. Currently, the *Codex Alimentarius* defines cheese as "*a ripened or unripened, soft, semi-hard, hard, or extra-hard, dehydrated milk-derived product in which the whey protein/casein ratio does not exceed that of milk*" [1]. Thus, cheese is the generic name for a group of milk-derived food products that come in a great variety of forms, sizes, textures, aromas, and tastes. The use of milk from distinct species (cows, sheep, goats, yaks, buffalos, moose, llamas) or their mixtures and the different technological operations employed in coagulation (e.g., acidification or the addition of animal rennet- or microbial- and plant-derived coagulants), the cutting of the coagulum (from rice grain to walnut size), whey drainage, washing, heating (from 30 °C to 55 °C), pressing, salting (between 1% and 5% NaCl), ripening, dehydration, immersion (in oil, wine or brine), wrapping (with ash or flour, etc.), and the addition of spices (pepper, cumin, clover, rosemary, aromatic herbs, garlic, etc.) or colorants (chlorophylls, paprika, annatto) make cheese one of the most diverse of all foodstuffs [2,3] (Figure 1).

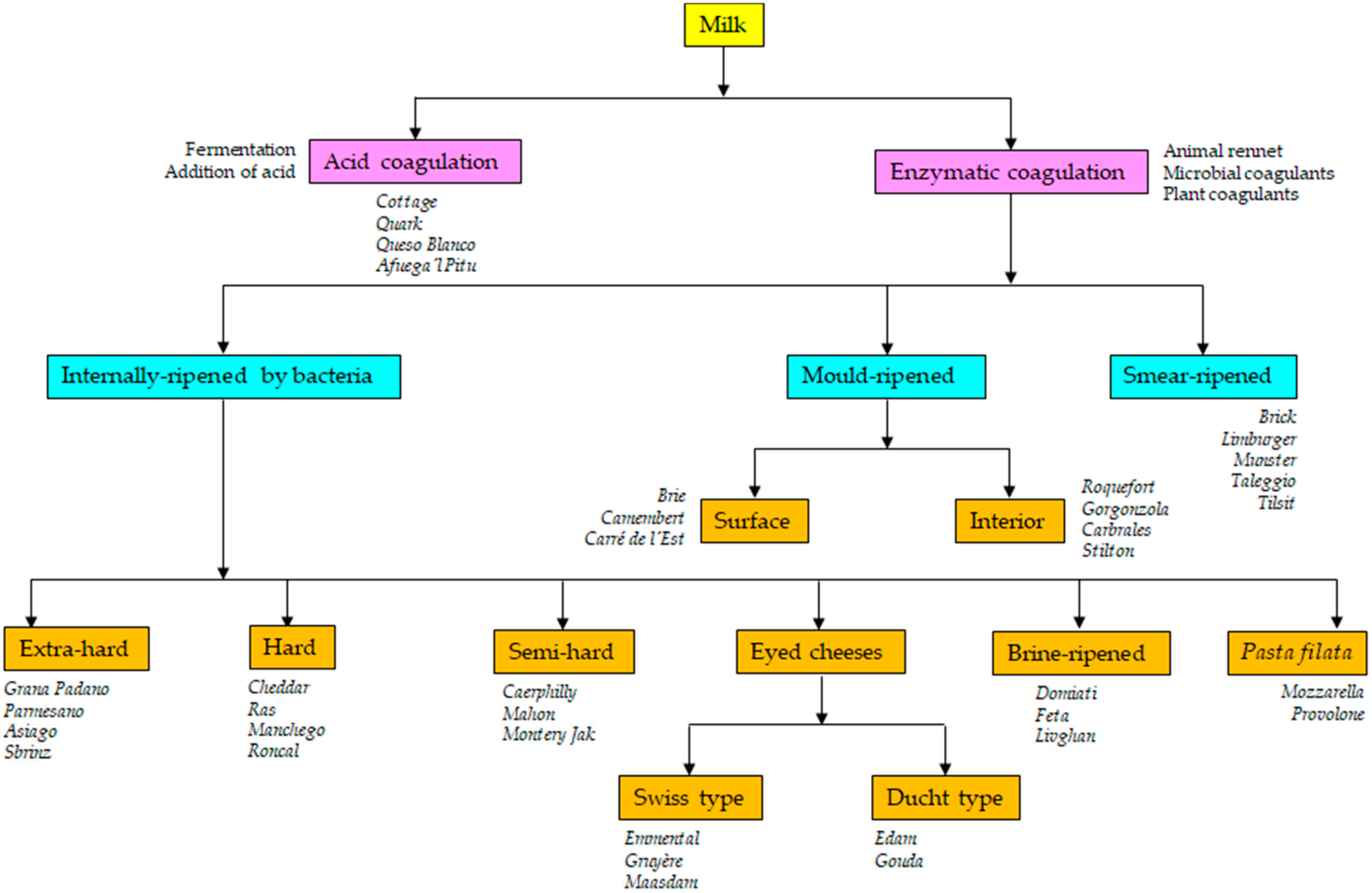

Figure 1. Schematic diagram of the cheese manufacturing processes and types of the resulting cheese varieties.

The sensorial properties of cheese depend on the milk type used, the feed given to the providing animal, the manufacturing practices involved, the ripening environment, the duration of ripening, and the type, numbers and activity of the microorganisms in the forming product [4,5]. Microorganisms are responsible for the fermentation of milk and for the many biochemical reactions occurring during manufacturing and ripening, which give rise to the distinctive cheese-associated textures and flavors.

In the wake of the booming amount of microbial data obtained through state-of-the-art molecular methods, this review presents updated knowledge on the composition of the cheese microbiota and summarizes the microbial interactions taking place in the cheese ecosystems. The review shows a strong focus on the biotic and abiotic factors driving the development and succession of the microbial populations and points out the potential use of this knowledge to improve the sensorial properties and safety concerns of cheese.

2. Cheese Starters and Adjunct Cultures

Milk can be coagulated by heating, by the formation or addition of acid, by the use of a natural coagulant (such as rennet), or a combination of these treatments (Figure 1). Spontaneous acidification is caused by the growth of lactic acid bacteria (LAB), a diverse bacterial group the members of which generate lactic acid as the main end-product of lactose fermentation. The typical LAB are arranged into the genera *Lactococcus*, *Lactobacillus*, *Leuconostoc*, and *Pediococcus* [6,7]. Via the action of complex anabolic and catabolic systems, the growth of LAB modifies the constituents of the milk (carbohydrates, proteins and lipids) [8]. These modifications do not involve nutritional or sensorial losses; rather, they increase the bioavailability and diversity of nutrients and improve the quality and complexity of flavor profiles [9]. LAB naturally present in milk or on manufacturing tools and in the environment [10–16] are still relied upon in many traditional fermentations [17–28]. However, improvement in milk hygiene (mainly by refrigeration and pasteurization practices) and the need for standardization have promoted the generalized use of starters [11,13], i.e., selected strains of different LAB species deliberately added to the milk to control the fermentation and standardize the quality of the fermented product (Table 1). Not surprisingly, in the search for improved starters, most microbial studies of cheese have focused on the isolation and characterization of new LAB strains of species such as *Streptococcus* (*S.*) *thermophilus*, *Lactococcus* (*Lc.*) *lactis*, *Lactobacillus* (*Lb.*) sp., and *Leuconostoc* (*Leuc.*) sp. [24,29–38]. In the industry, however, the term "starter" refers to all microorganisms added to the milk with a technological purpose, e.g., for improving the appearance, texture, and/or flavor of the final product, and thus also covers LAB species not involved in acidification, the so-called non-starter LAB (NSLAB) [39,40]. In certain cheeses, it also covers bacteria of the genera *Propionibacterium* (Emmental, Gruyère), *Brevibacterium*, and *Corynebacterium* (smear-ripened cheeses), molds and yeasts such as *Penicillium* (*P.*) *roqueforti* (blue-veined varieties), *P. camemberti* (white moldy varieties), *Geotrichum* (*G.*) *candidum*, *Debaryomyces* (*D.*) *hansenii* (moldy and smear-ripened cheeses), and others [39,40]. These secondary types of microorganisms are usually referred to as adjunct and/or ripening cultures (Table 1).

Table 1. Current common species used as "starters" in industrial dairy fermentations.

Microbial Group/Species	Cheese	Type of Starter	Main Role/s
Lactic acid bacteria			
Lc. lactis subsp. *lactis* *Lc. lactis* subsp. *cremoris*	Most cheeses	Primary	Acidification, flavor development
S. thermophilus *Lb. delbrueckii* subsp. *lactis*	Italian and Swiss types	Primary	Acidification, flavor development
Leuc. mesenteroides subsp. *cremoris* *Leuc. lactis*	Soft and semi-hard	Secondary/adjunct	Flavor development, CO_2 production
Lb. helveticus	Semi-hard, hard	Secondary/adjunct	Flavor development, health benefits
Lb. casei/Lb. paracasei	Artisanal	Secondary/adjunct	Flavor development
Lb. plantarum	Artisanal	Secondary/adjunct	Flavor development

Table 1. *Cont.*

Microbial Group/Species	Cheese	Type of Starter	Main Role/s
Propionibacteria			
Propionibacterium freudenreichii	Swiss-type	Secondary/ripening	Hole formation, flavor development
Other bacteria			
Brevibacterium linens	Smear-ripened	Secondary/ripening	Color, flavor development
Corynebacterium casei	Smear-ripened	Secondary/ripening	Flavor development
Fungi			
P. camemberti	White moldy	Secondary/ripening	Aspect, texture, and flavor development
P. roqueforti	Blue-veined	Secondary/ripening	
G. candidum	Smear-ripened	Secondary/ripening	

Compiled and modified from Fox et al. [39] and Parente and Cogan [40].

3. Cheese Microbiology

The microbial composition of cheese and the microbial succession of the microorganisms in the cheese matrix have traditionally been assessed by culturing methods [25,26,41–49]. These rely on the isolation and cultivation of microorganisms before their identification and typing. However, culturing has repeatedly been shown unreliable for the exhaustive microbial characterization of many food ecosystems [50–52]. For example, the selective isolation of certain microbial taxa may require unknown growth factors and/or growth conditions that are not reproduced in the laboratory media [53]. Besides, cheese can have a low pH, a reduced a_w, and is commonly kept under harsh storage conditions (e.g., at low temperatures or in strong brine), all of which might leave certain microbes in a physiologically viable but non-cultivable state [54]. Further, microbes present in low numbers can be outcompeted in culture by numerically abundant species, impeding the effective detection of the former [45,55–57]. The culture techniques can therefore underestimate the microbial diversity present and sometimes even fail to detect some majority microbial groups.

Helping to overcome the problems of culturing, numerous culture-independent, molecular methods based on the amplification of nucleic acids by polymerase chain reaction (PCR) have been developed, such as denaturing gradient gel electrophoresis (DGGE) [23,57–61], temporal temperature gradient electrophoresis (TTGE) [45,62], real-time quantitative PCR (qPCR) [63,64], single strand conformation polymorphism (SSCP) [65,66], the construction and analysis of gene libraries [46,66], and others [67]. The basis, similarities, differences and main outputs of such techniques, all of which have been extensively used to investigate the microbiology of cheese and dairy systems, are schematically depicted in Figure 2. As an example of the value of using such molecular techniques, *Leuc. lactis* and *Mycoplasma agalactiae*, constituting subdominant populations in two farmhouse goats' milk cheeses and detected by PCR-TTGE, could never be recovered from cultures [45]. Similarly, although many *Arthrobacter* and *Brevibacterium* species were detected by PCR-DGGE in the smear-ripened Limburger cheese, only strains of *Arthrobacter* (*Arthr.*) *arilaitensis* and *Brevibacterium* (*Brev.*) *aurantiacum* have been retrieved by culturing [42]. Further, during the microbial typing of natural whey cultures for water-buffalo Mozzarella cheese production, *Lb. fermentum*, a majority population as judging by PCR-DGGE, was not recovered in culture [58]. Nonetheless, different LAB species have been found dominant in most cheeses both by culturing and molecular techniques, but only the latter were able to associate cheese ecosystems with occasional subdominant populations and minority microorganisms such as *Agrococcus* and *Leucobacter* [56], *Massilia* sp. [57], and *Bifidobacterium* sp. [68].

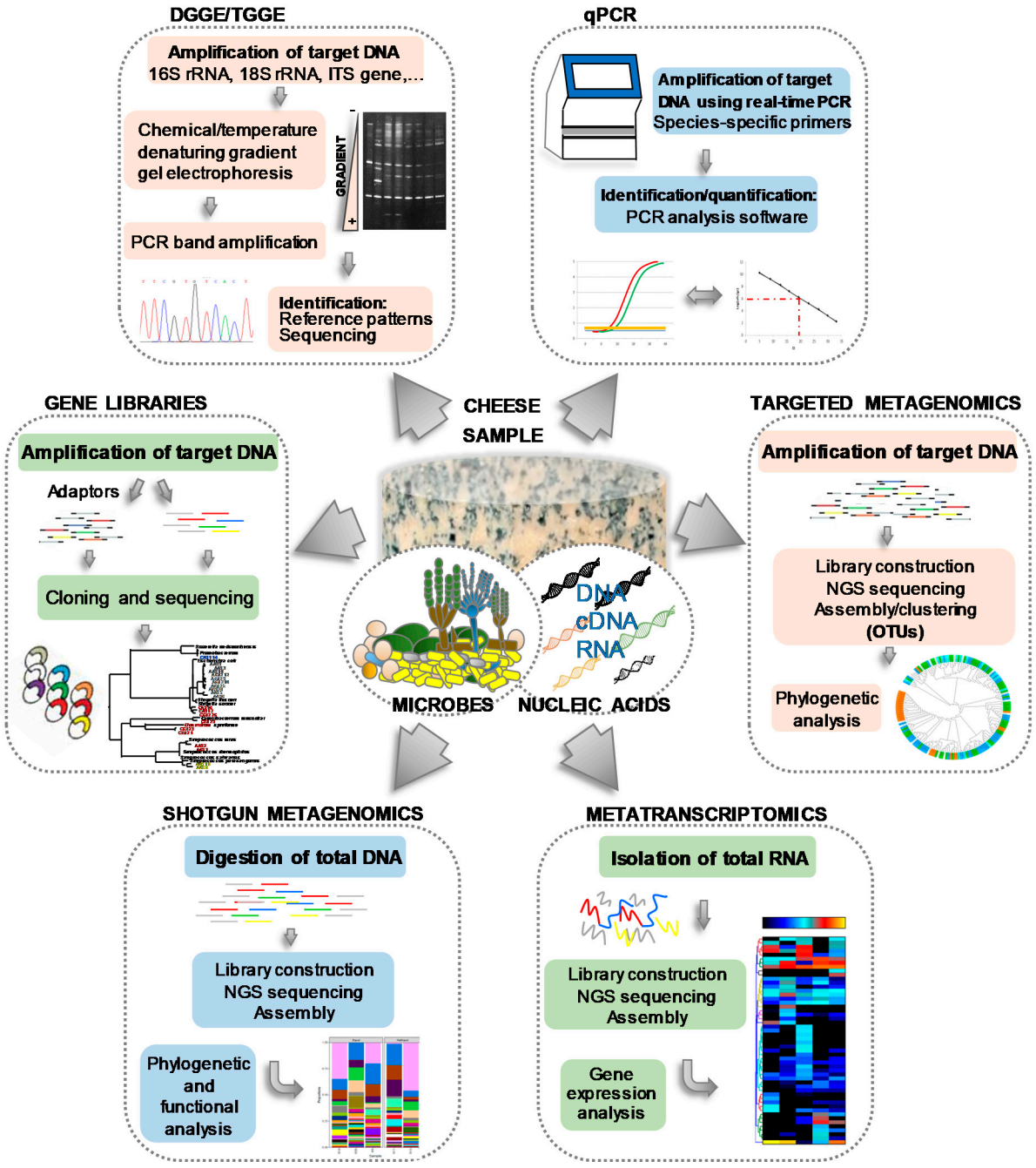

Figure 2. Flow chart of different microbial culture-independent molecular methods, including the main steps and final outputs, applied in cheese microbiology.

More recently, the advent of high throughput sequencing (HTS) of DNA has promoted the emergence of new, culture-independent technologies [69–73]. For metagenomics purposes, HTS can be used in two distinct ways: gene-specific sequencing (targeted sequencing) and the sequencing of all the microbial nucleic acids present (shotgun sequencing) (Figure 2). Compared to earlier molecular methods, HTS techniques analyze a vastly greater number of nucleic acid molecules, allowing for a much more comprehensive description of a cheese's microbial constituents. After a pioneering use of pyrosequencing [68,74–77], Ilumina [73,78] and PacBio [79,80] technologies are currently the gold standard HTS techniques. Surprisingly, HTS has uncovered an unprecedented microbial diversity in cheeses. For example, 132 genera of the Bacteria and Archaea domains have been identified on the surface of a Swiss smear-ripened cheese [81]. Also, 238 species belonging to 14 phyla

and 140 genera were recently identified in a Kazakh cheese [80], and up to 574 operational taxonomic units (OTUs) have been reported in traditional Mexican Cotija cheese [82].

LAB reads usually account for > 90% of the sequences (*Lactobacillus, Leuconostoc, Weissella, Enterococcus*, and *Lactococcus*) detected within the inner part of the cheese, but only less than 30% of reads from certain surfaces [83]. The HTS-based discovery of sequences belonging to microbes previously undetected in the dairy environment [84,85] may allow for the isolation and characterization of new biotypes by conventional [86] and novel cultivation techniques ("culturomics") [53,87]. Further, the integration of data from culturing and culture-independent techniques (including genomics, metagenomics, metatranscriptomics, and metabolomics) is expected to provide insights into the cause–effect relationships between microbes and the metabolites that shape the sensorial descriptors of cheese, such as organic acids, fatty acids, amino acids, volatile compounds, etc. [88,89]. Certainly, while the inventory and succession of bacteria, yeasts, and molds in some cheeses are known, the functional features of the different populations are yet to be understood. By and large, most studies have been descriptive, and relatively little is known about the mechanisms that govern the architecture and dynamics of microbial populations or the molecular interactions between their members. Indeed, the activity in the cheese matrix of some uncultured/uncharacterized microbes may have a huge impact on the overall quality and safety of some cheeses [90,91]. However, understanding the technological importance and biological significance of such phenotypic microbial diversity and the genetic redundancy in cheese remains a challenge.

4. The Cheese Microbiota

Whether fermented in a natural manner, or with the aid of starter and/or adjunct cultures, most cheeses contain a complex mixture of microbial populations—including technologically-relevant, spoilage, opportunistic and pathogenic organisms—that develops and changes throughout manufacturing and ripening [11,92,93]. All these microbes constitute the microbiota of the cheeses (Table 2). Both intrinsic (substrates, vitamins, cofactors, the presence of inhibitory/activator compounds, pH, redox potential) and extrinsic factors (oxygen availability, temperature, salt, relative humidity) drive the numbers and spatial and temporal distribution of the members of the microbiota [89,94]. The populations of the microbiota are composed of prokaryotic *Archaea* and *Bacteria*, eukaryotic yeasts and fungi [74,81,82,95,96], and viruses (mainly bacteriophages) [97–99]. The microbiota of cheese can be as simple as that of yogurt and other kinds of fermented milks, with perhaps just one or a very small number of LAB species present, such as in Petit-Suisse (*S. thermophilus* and *Lb. delbrueckii* subsp. *bulgaricus*) [100] and Quark (*Lc. lactis* subsp. *lactis* and *Lc. lactis* subsp. *cremoris*) [101]. More often, however, the cheese microbiota is composed of a consortium of diverse microorganisms and varies widely from one variety to another, although the dominant microbial types for each cheese type (soft, hard, natural rind, smear-ripened, blue-veined, etc.) are usually similar [42,102–104]. The microbiota becomes particularly complex in blue-veined and smear-ripened varieties (Table 2). As in other ecosystems, the diversity of the microbiota in cheese is governed by classical ecological processes, such as dispersion, diversification, environmental selection, and ecological drift (Figure 3). Microbial diversity and numbers are also influenced by the environmental interaction of biotic (natural fermentation, use or not of starters, presence of contaminating microbes and microbial metabolites) and abiotic factors (technological processes and environmental conditions), which modulate the implantation, development and, more importantly, the activity of the different microbes (Figure 3). Together, these variables determine the growth and function of the microorganisms and, therefore, some of the key biochemical changes they drive during ripening that lead to the unique appearance, texture, aroma and taste properties of each cheese variety, as well as their safety quality [4,8,105].

Table 2. Non-exhaustive compilation of microbial studies of traditional cheeses, technologies applied, and dominant populations identified or detected.

Cheese/Type, Country (Milk Type)	Technique	Microbial Target	No. of Specimens	Main Families/Genera/Species (Relative Abundance); Sampling Point	Reference
Culturing					
Bryndza/soft Feta-type, Slovakia (Sheep)	Culturing	Fungi	5 species	*Geotrichum candidum* > *Kluyveromyces marxianus* > *Pichia fermentans* > *Candida inconspicua* > *Trichosporon cutaneum*	Laurencík et al. [106]
Cabrales/blue-veined, Spain (Cow, sheep, and goat)	Culturing	LAB	15 species	*Lc. lactis* subsp. *lactis* > *Lb. plantarum* > *Leuc. mesenteroides* > *Leuc. citreum* > *Enterococcus* > *Lb. paracasei*	Flórez et al. [107]
Gubbeen/smear-ripened, Ireland (Cow)	Culturing	Corynebacteria	39 species	*Corynebacterium casei* (50.2%) > *Corynebacterium mooreparkense* (26%) > *Microbacterium gubbeenense* (12.8%); cheese rind	Brennan et al. [48]
May bryndza/soft, Slovakia (Sheep)	Culturing	Bacteria Fungi	5 species 17 species	*Lc. lactis* subsp. *cremoris* > *Lc. lactis* subsp. *lactis* > *Mannheimia glucosida* *G. candidum* > *Penicillium* > *Beauveria brongniartii* > *Alternaria alternata*	Pangallo et al. [108]
Rinds of 33 cheeses/smear-ripened, various countries (Cow, sheep, or goat)	Culturing, sequencing	Microbes	104 bacterial genera, 39 fungal genera	*Staphylococcus* (78%) > *Brevibacterium* (75%) > *Corynebacterium* (75%) > *Arthrobacter* (66%) > *Lactococcus* (50%) > *Enterococcus* (41%) > *Brachybacterium* (38%) > *Microbacterium* (38%) > *Psychrobacter* (33%) > *Halomonas* (31%) > *Lactobacillus* (25%) > *Streptococcus* (22%) > *Marinilactibacillus* (22%) > *Pseudoalteromonas* (22%) > *Agrococcus* (19%) > *Micrococcus* (19%) > *Vibrio* (19%) > *Vagococcus* (16%) > *Facklamia* (16%) *Debaryomyces* (86%) > *Yarrowia* (57%) > *Candida* (54%) > *Geotrichum* (49%) > *Kluyveromyces* (32%) > *Pichia* (22%) > *Penicillium* (19%) > *Scopulariopsis* (8%) > *Fusarium* (8%)	Irlinger et al. [12]
Scamorza Altamurana/pasta filata, Italy (Cow)	Culturing	LAB	10 species	*Lb. delbrueckii* > *Streptococcus macedonicus* > *S. thermophilus* > *Enterococcus durans* > *Lb. fermentum* > *Lb. paracasei*	Baruzzi et al. [28]
Culturing and molecular methods					
Casín/kneaded, Spain (Cow)	Culturing DGGE	Bacteria Bacteria (V1-V2 16S rDNA)	14 species 14 OTUs	*Lc. lactis* subsp. *lactis* > *Lactococcus garvieae* > *Staphylococcus saprophyticus* > *Klebsiella* > *Lb. plantarum* *Lc. lactis*, *Streptococcus parauberis*, *S. thermophilus*, *Lc. garvieae*, *Lb. plantarum*, *Enterobacter*, *Corynebacterium variabile*, *Lb. paracasei*, *Macrococcus caseolyticus*	Alegría et al. [25]

Table 2. *Cont.*

Cheese/Type, Country (Milk Type)	Technique	Microbial Target	No. of Specimens	Main Families/Genera/Species (Relative Abundance); Sampling Point	Reference
Castelmagno/semi-hard, Italy (Cow)	Culturing PCR-DGGE	LAB Bacteria (V1 16S rDNA)	11 species 7 OTUs	*Lc. lactis* subsp. *lactis* > *Lb. plantarum* > *Lc. paracasei* >*Enterococcus faecium* >*E. durans* *Lb. plantarum, Lb. kefiranofaciens, Lactobacillus, Lc. lactis, Streptococcus agalactiae, M. caseolyticus*	Dolci et al. [44]
Cueva de la Magahá/hard, Spain (Goat)	Culturing PCR-TTGE	Bacteria Bacteria (V3 16S rDNA)	10 species 8 species	*Lb. paracasei* > *Lb. plantarum* > *Lb. brevis* > *Lactobacillus* > *Enterococcus* *Lb. plantarum, Lb. brevis, Lc. Lactis, S. thermophilus, Staphylococcus equorum, Lb. curvatus, Lb. paracasei*	Martín-Platero et al. [45]
Grana Padano/hard, Italy (Cow)	LH-PCR	LAB	6 species	*Lb. rhamnosus* > *Lb. paracasei* > *Lb. delbrueckii* > *Pediococcus acidilactici*	Santarelli et al. [22]
Livarot/smear-ripened, France (Cow)	Culturing Cloning	Bacteria/yeasts Bacteria (V4 16S rDNA)	8 bacteria, 5 yeasts species 8 species	*M. gubbeenense* > *Leucobacter komagatae* > *Halomonas*; cheese rind *Candida catenulata* > *Candida intermedia* > *G. candidum* > *Geotrichum* > *Yarrowia lipolytica*; cheese rind*Halomonas* > *L. komagatae* > *M. gubbeenense*; cheese rind	Mounier et al. [43]
Nottinghamshire/blue-veined, UK (Cow)	Culturing PCR-DGGE	Bacteria Bacteria (V3, V4-V5, V6-V8 16S rDNA)	12 species 11 OTUs	*Lc. lactis* subsp. *lactis* > *E. faecalis* > *Kokuria* > *Lactobacillus* *Lc. lactis, Lb. plantarum, Staph. equorum*	Yunita and Dodd [55]
Ragusano/pasta filata, Italy (Cow)	PCR-DGGE	Bacteria (V6-V8, V1-V3 16S rDNA or rRNA)	12 species	*S. thermophilus, Lb. fermentum, Lb. delbrueckii, Lc. lactis, Leuc. mesenteroides, Lb. casei, Enterococcus hirae* > *E. faecalis*	Randazzo et al. [61]
Salers/semi-hard, France (Cow)	PCR-SSCP	Bacteria (V2 16S rDNA)	9 OTUs	*E. faecium, Leuconostoc, Enterobacteriaceae, Bacillus thuringiensis, S. thermophilus, Leuc. pseudomesenteroides, Lb. pentosus, Corynebacterium variabilis, Brachybacterium nesterenkovii*	Duthoit et al. [66]

Table 2. *Cont.*

Cheese/Type, Country (Milk Type)	Technique	Microbial Target	No. of Specimens	Main Families/Genera/Species (Relative Abundance); Sampling Point	Reference
Saint Nectaire/smear-ripened, France (Cow)	Culturing SSCP-PCR	Bacteria Bacteria	21 species 12 OTUs	*Lc. lactis* > *Staphylococcus fleurettii* > *E. faecalis* > *S. thermophilus* > *Marinilactibacillus psychrotolerans* > *Chryseobacterium* > *Klebsiella* *Lc. lactis*, *S. thermophilus*, *Clostridium confusum*, *Nocardioides dubius*, *Arthrobacter psychrolactophilus*, *Enterobacter agglomerans*	Delbès et al. [46]
Molecular methods/high throughput sequencing					
Artisan cheeses/various, Ireland (Cow, goat, or sheep)	Pyrosequencing	Bacteria (V4 16S rDNA)	5 phyla 21 genera	*Lactococcus* (50–90%) > *Lactobacillus* > *Leuconostoc* > *Pseudomonas* > *Psychrobacter* > *Staphylococcus* > *Arthrobacter* > *Faecalibacterium*; common to 62 cheeses	Quigley et al. [76]
Buryatian/soft, Kazakhstan (Cow)	PacBio sequencing	Microbes	7 phyla, 82 genera, 145 species	*Lactococcus* (51.46%) > *Streptococcus* (17.81%) > *Pseudomonas* (5.48%) > *Acetobacter* (4.83%) > *Klebsiella* (3.36%) > *Lactobacillus* (2.36%) > *Acinetobacter* (1.84%) > *Raoultella* (1.63%)	Jin et al. [79]
Canestrato Pugliese/hard, Italy (Sheep)	Pyrosequencing	Bacteria (V1-V3 16S rDNA)	28 genera	*Lactococcus* (87.2%) > *Lactobacillus* (4.8%; mainly *Lb. plantarum* and *Lb. sakei*) > *Leuconostoc* (3.9%)	De Pasquale et al. [109]
Cheddar/semi-hard, UK (Cow)	Illumina sequencing	Bacteria (V4 16S rDNA)	159 OTUs	*Streptococcus* > *Lactococcus* > *Lactobacillus* > *Staphylococcus* (70%); interior	Afshari et al. [110]
Gouda-like cheese/semi-hard, USA (Cow)	Illumina sequencing	Bacteria (V4 16S rDNA)	36 genera	*Bacillaceae* > *Lactococcus* > *Lactobacillus* > *Streptococcus* > *Staphylococcus*	Salazar et al. [111]
Cotija/hard, Mexico (Cow)	Illumina sequencing	Microbes	31 phyla, 574 genera	*Lb. plantarum* > *Leuc. mesenteroides* > *Weissella paramesenteroides* (>80%) *Aerococcus* > *Enterococcus* > *Lactococcus* > *Staphylococcus* (<10%)	Escobar-Zepeda et al. [82]
Grana/hard, Italy (Cow)	RT-PCR-DGGE Pyrosequencing	Bacteria (V1 16S rDNA) Bacteria (V1-V3 16S rDNA)	16 OTUs 25 genera	*Lb. helveticus*, *Lb. delbrueckii*, *S. thermophilus*, *Lb. acidophilus*, *Lb. rhamnosus*, *Acetobacter baumanii*, *Propionibacterium* *Lb. helveticus* > *Propionibacterium* > *Lb. delbrueckiii* > *Lb. casei* > *Lb. rhamnosus* > *S. thermophilus* > *Staphylococcus* > *Lb. brevis*	Alessandria et al. [95]

Table 2. *Cont.*

Cheese/Type, Country (Milk Type)	Technique	Microbial Target	No. of Specimens	Main Families/Genera/Species (Relative Abundance); Sampling Point	Reference
Artisanal cheeses/soft, Kazakhstan (Cow)	PacBio sequencing	Microbes	14 phyla, 140 genera, 238 species	*Lc. lactis* (28.93%) > *Lb. helveticus* (26.43%) > *S. thermophilus* (12.18%) > *Lb. delbrueckii* (12.15%)	Li et al. [80]
Ocosingo/semi-hard, Mexico (Cow)	Pyrosequencing	Bacteria (V1 16S rDNA)	162 OTUs	*S. thermophilus* > *Lc. lactis* > *Lb. helveticus* > *Lb. delbrueckii* > *Lb. plantarum* (70%); interior	Aldrete-Tapia et al. [17]
Tomme d'Orchies/semi-hard, France (Cow)	Illumina sequencing	Bacteria (V1-V3 16S rDNA)	10 species core, 21 species surface	*Lactococcuss* > *Streptococcus* (66%); interior *Lactobacillus* > *Lactococcus* > *Corynebacterium* > *Micrococcales* > *Psychrobacter* (80%); surface	Ceugniez et al. [83]
Tomme d'Orchies/semi-hard, France (Cow)	Illumina sequencing	Fungi 5.8S-ITS2	30 OTUs	*Y. lipolytica* > *G. candidum*/ *Galactomyces geotrichum* (99%); interior *Y. lipolytica* > *G. candidum*/ *Galactomyces geotrichum* (98%); surface	Ceugniez et al. [112]

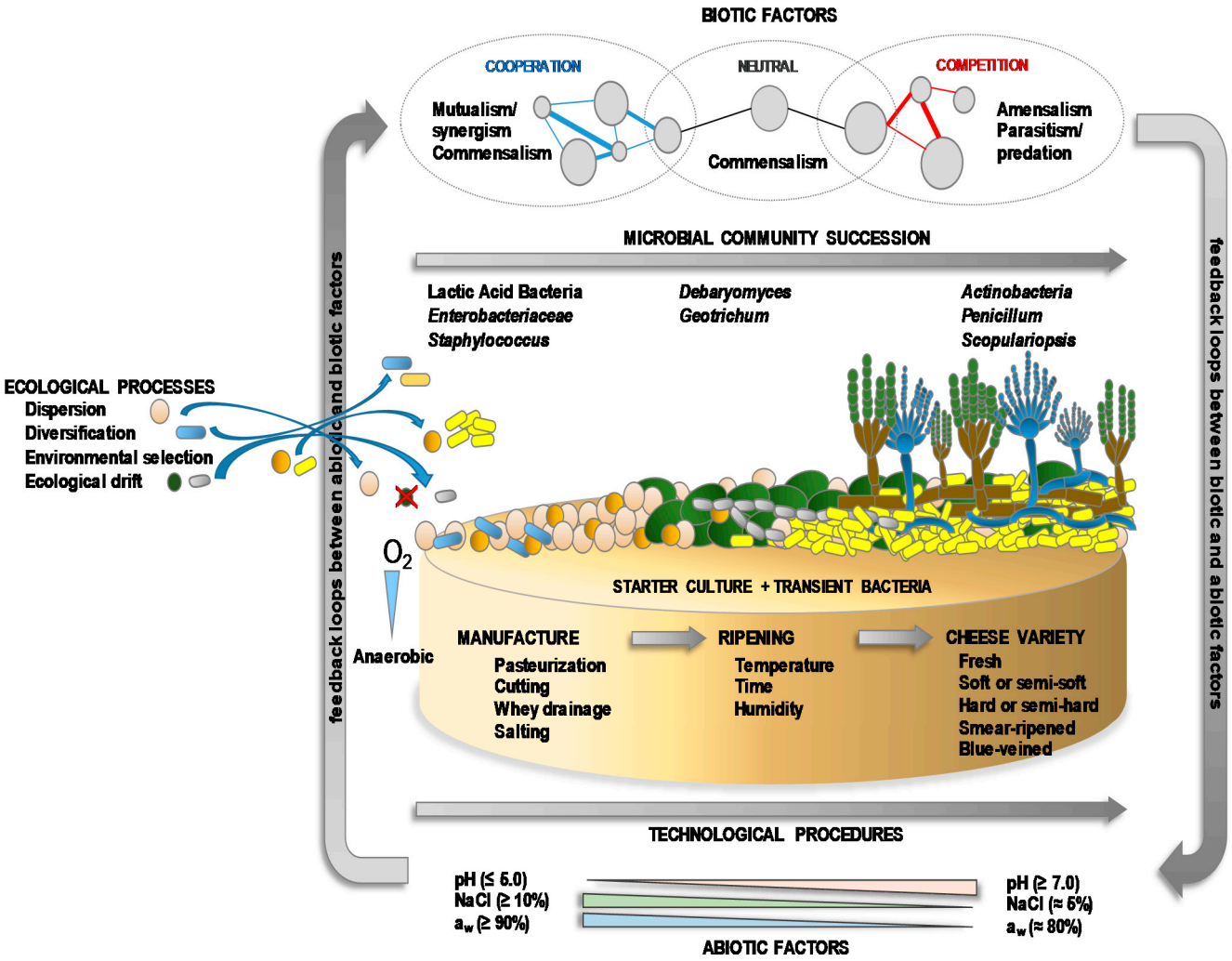

Figure 3. A succession of the microbial communities of the microbiota at the cheese surface, and ecological processes and environmental biotic and abiotic factors (including technological procedures) that influence microbial colonization, development and activity.

Cheese bacteria belong mainly to the phyla *Firmicutes* (LAB, enterococci, staphylococci), *Actinobacteria* (corynebacteria, propionibacteria, bifidobacteria), and *Proteobacteria* (enterobacteria) [55,56,83,104,107]. The archaeal taxa include members of *Thermocladium, Sulfurisphaera, Methanohalobium,* and others; these are minority populations (< 0.5% relative abundance) and have only ever been detected by molecular methods [57,81,82]. Among the eukaryotes, the dominant yeasts belong to the genera *Geotrichum, Debaryomyces, Kluyveromyces, Candida,* and *Yarrowia*, and the filamentous fungi are molds such as *P. camemberti, P. roqueforti* and other *Penicillium* species, which are abundant in mold-ripened cheese varieties [12,47,106,112,113]. Other filamentous fungi such as *Fusarium domesticum, Scopulariopsis* (*Sc.*) *flava* and *Sc. casei* are also found in low numbers on the surface of most cheeses [12,14,96]. Except for *P. roqueforti*, all these other mold species are only known from cheese, suggesting they are adapted ("domesticated") to this particular habitat. In particular, *P. camemberti* derives from the wild ancestor *Penicillium commune* in a quick adaptation process that involves reduced reproductive output, reduced mycotoxin production, reduced pigmentation and, significantly, a change in the volatile compound profile from earthy to cheesy [114]. The genetic basis of this rapid "evolution" has proven to be through gene regulation instead of genome changes [114]. *Lc. lactis* subpopulations of the *lactis* and *cremoris* subspecies in dairy environments are also thought to be adapted

through domestication processes [115,116]. These, and the domesticated strains of other LAB species found only in milk and dairy products, seem to have emerged recently due to the selective pressure imposed by the dairy technologies [117].

Though highly variable between varieties, the concentration of bacteria in ripened cheese may exceed 10^9 colony forming units (cfu)/g [5,25,108,118], while those of yeasts and filamentous fungi range widely between 10^2 and 10^7 cfu/g [5,28,96,106,113,119]. Depending on the microbial taxon, maximum numbers are reached by the end of the fermentation (e.g., *Lc. lactis*), between day 7 to 17 (e.g., *Lactobacillus* spp.) after one to two months of ripening (e.g., filamentous fungi). Once the highest level is reached, numbers are declining slightly but consistently afterward. Variations in the composition and/or dynamics of the microbial communities making up the typical microbiota of a given cheese can lead to serious technological and sensorial defects [84,85,120–122] and even pose food safety risks [123,124].

5. Microbial Interactions in Cheese

In nature, microorganisms live in complex communities, in which different direct and indirect, cooperative and competitive microbial interactions can occur (Figure 3). Microbial interactions are mediated through a variety of molecular and physiological mechanisms, of which trophic interactions (cross-feeding) and the exchange of metabolites are the most typical. Trophic food chains enable multiple groups of organisms to survive on limited resources, increasing community diversity [125,126]. Conversely, some microbes can be inhibited or killed by metabolic substances or antimicrobial compounds produced by other components of the microbiota [127–129]. In general, the interactions between the different microorganisms impact the final composition and diversity of the cheese microbiota, but particularly its functionality [130,131]. In the context of milk fermentation, direct interactions refer to parasitism and apply mostly to phage-bacteria predation [132]. Under the changing environmental conditions throughout manufacture and ripening, bacteriophages are considered key players in the dynamics of the cheese microbial communities [133]. Phage predation ensures bacterial diversity by suppressing abundant strains (by the "kill the winner" theory), stabilizing the overall functionality of the host community [134]. Phages may have a tremendous effect on the fermentation, in which LAB populations need to attain high cell numbers in a very short time [132]. A fermentation failure leads usually to a subsequent improper ripening process downgrading the sensory properties of the final product. Regardless of this importance, due to the inanimate living nature of the phages, the direct bacteriophage–bacteria interactions are outside the scope of this review. Many different types of indirect interactions between the other microbial types exist [135,136], although, as in other ecosystems, the four main types in cheese involve competition, amensalism, commensalism, and mutualism [137–140].

5.1. Competition

In competition, two or more microorganisms compete for nutrient and energy resources in a manner that negatively affects both. The success of LAB in milk is due to their efficient use of the nutrients found in this medium, which include lactose (a rare sugar outside milk, the utilization of which requires specific transport and degradation machinery [141]), and the ability to degrade milk proteins (caseins) and efficiently take up the released amino acids and peptides [140]. Other organisms are limited by the inability of using lactose and/or the small amounts of freely available nitrogenous substrates [142,143]. Iron and zinc are also thought to be limiting micronutrients in dairy products [84]. Some microorganisms, such as *Arthrobacter, Corynebacterium*, yeasts, etc., produce siderophores to help take up these essential trace elements, while siderophore-deficient bacteria such as *Brevibacterium* and *Microbacterium*, etc., have molecular systems that help them to "steal" siderophores from their producers [84,144]. Understanding these interactions is essential, for instance, to selecting starter species and strains (or mixtures of strains) with efficient metal acquisition systems [145,146], which will allow them to strive for growth in dairy systems.

5.2. Amensalism

Amensalism involves interactions in which one type of microorganism negatively affects another without being affected itself. This type of relationship is commonly seen in dairy fermentations, where strains of many LAB species produce organic acids (lactic and acetic acids) that are effective inhibitors of susceptible microorganisms [128,129]. In addition to reducing the pH when released into the surrounding medium, they also have a direct inhibitory effect resulting from their undissociated forms by diffusing through the cell membranes and releasing H+ ions that acidify the cell cytoplasm [147]. Some other LAB antimicrobials, such as bacteriocins, H_2O_2, and fatty acids, are also thought to inhibit the growth of some organisms [148]. Bacteriocin-producing strains typically synthesize dedicated systems that protect them from these products' harmful effects. In practice, bacteriocin-producing strains are used as "protective cultures" [149] to inhibit the development of pathogens and spoilage microorganisms in cheese. Indeed, they have been tested as inhibitors of *Listeria* (*L.*) *monocytogenes* [150–156], *Staph. aureus* [157,158], *Salmonella* sp. [159], *Clostridium* sp. [160–162], and other undesirable microbes [163]. Despite their technological use, bacteriocins may have physiological functions beyond their inhibitory activity [164,165]. Some authors [166] have suggested that subinhibitory levels may play subtle roles in guiding the succession of microbes in food fermentations.

Occasionally, the antimicrobial activity is associated with a microbial consortium rather than any single strain. For example, strong antilisterial activity exerted by some undefined consortia from the rind of smear-ripened cheeses has been repeatedly reported [167–171]. Via addition and erosion experiments (i.e., adding or removing one strain at a time from a mixture), attempts have been made to establish the "minimum community" showing an inhibitory property [169]. Interestingly, some minimal communities have been shown to exert greater antilisterial activity than the initial complex smear. After partial purification, an antimicrobial produced by one such minimum community proved to be a small, extremely thermo- and protease-stable molecule [168].

Certain LAB also have antifungal activity [147]. The nature and quantity of antifungal compounds produced are species- and strain-dependent. Organic acids (phenyllactic, hydroxyphenyllactic), fatty acids (decanoic, coriolic), cyclopeptides, hydrogen peroxide, and diacetyl have all been found to inhibit certain fungi [128]. The production of antifungal compounds, however, is not limited to bacteria. As such, the yeast *Williopsis saturnus* (with the killer phenotype) has been reported to inhibit the galactose-fermenting spoilage yeasts *Saccharomyces* (*Sc.*) *cerevisiae* and *Kluyveromyces* (*K.*) *marxianus* [172]. Negative yeast–yeast interactions unrelated to antimicrobials, but rather of a metabolic nature, have also been reported. In co-cultures of *D. hansenii* and *Yarrowia* (*Y.*) *lipolytica*, the latter yeast causes a shift from respiratory to fermentative metabolism in the former [173].

5.3. Commensalism

Commensalism occurs when a microorganism in a mixture is favored by the interactions that occur in that mixture, while other organisms experience neither negative nor positive effects. It has long been recognized that the proteolytic activity of proteinase-positive LAB cultures enables non-proteolytic species and strains to grow in milk [174,175]. The same interaction has also been reported between the LAB components of the traditional Dutch starter culture known as *Ur* [133]. In this starter, culturing and typing techniques have identified eight genetic lineages as the microbial components, including five strains of *Lc. lactis* subsp. *cremoris*, two of *Lc. lactis* subsp. *lactis* biovar *diacetylactis*, and one of *Leuc. mesenteroides*. Genome analysis and *in silico* reconstruction of metabolic maps of the different species and strains of the consortium suggested that γ-aminobutyric acid (GABA) excreted by *Lc. lactis* as part of its acid stress response might serve as a substrate for succinate formation by *Leuc. mesenteroides*. In contrast, this species did not appear to contribute to the growth of *Lc. lactis* strains [133]. Likewise, in Swiss-type cheeses, propionic acid bacteria (PAB) utilize the lactate produced by LAB, generating the typical "eyes" of these cheeses [2,4], without any apparent benefit for the latter population. The presence of lactate

alone, however, cannot explain all the beneficial effects of LAB on PAB. The growth of the latter bacteria might also be enhanced by amino acids and peptides released by the LAB proteolytic system [176]. Similarly, the stimulation of LAB growth by yeasts without apparent profit of the eukaryotic microorganisms has also been reported [177–179]. In French *Cantalet* cheese, the use of yeasts as adjunct cultures has been found to promote the survival of *Lc. lactis* cells during ripening, and to enhance the formation of the cheese's aroma [180]. This relationship might not be strictly commensal, however, since the yeasts might also benefit from LAB growth by using the glucose and/or galactose sugars released by some LAB species [177].

The regulation of color development in cheese rinds of a Muenster-type cheese by *Brevibacterium* (*Brev.*) *linens* via the activity of accompanying yeast species may, however, be understood as an outcome of true commensalism [181].

5.4. Mutualism

Mutualism is the relationship in which all the microorganisms involved benefit from their interactions. The most typical mutualistic interplay between LAB bacteria in dairy products is the so-called "protocooperation" that takes place in yogurt between *S. thermophilus* and *Lb. delbrueckii* subsp. *bulgaricus* [140,166]. This relies on casein proteolysis by *Lb. delbrueckii* subsp. *bulgaricus* via its surface caseinolytic proteinase PrtB, whose activity supplies amino acids to *S. thermophilus*. This latter bacterium, in turn, provides formic acid and carbon dioxide to the former organism [182]. Recently, it has been shown that urease activity in *S. thermophilus* is also essential in this cooperation [183]. Urease deficiency causes a shortage of ammonium and CO_2, compounds that affect the growth of *S. thermophilus* and *Lb. delbrueckii* subsp. *bulgaricus*, respectively. Additional interactions between the two microbes might include the supply of purine precursors (xanthine, uracil) by *Lb. delbrueckii* subsp. *bulgaricus* to *S. thermophilus*, and a reduction in the formation of reactive oxygen species (ROS) by *S. thermophilus* in response to H_2O_2 production by *Lb. delbrueckii* subsp. *bulgaricus* via the Fenton reaction [166]. Cooperation between other LAB species, such as that seen between *Lc. lactis* and *Lb. casei* in the proteolysis of milk proteins during cheese ripening, has also been reported [184].

Cooperative cross-feeding between LAB and yeast species isolated from cheese has been abundantly described [185,186]. Yeasts can provide LAB with essential vitamins [180] or with carbon (2-oxoglutarate) and nitrogen (amino acids) sources, while LAB can provide lactic acid to non-lactose fermenting yeasts as a preferred energy substrate [187,188]. A better understanding of the metabolic activities of yeasts and LAB species and their possible interactions in cheese rind has recently been gained by combining the results of metagenomic, metatranscriptomic, and metabolomic analyses [189]. In the rind of a cheese model involving a synthetic microbiota composed of *Lc. lactis*, *Brev. aurantiacum*, *Glutamicibacter* (*G.*) *arilaitensis* (formerly *Arthr. arilaitensis*), *Corynebacterium casei*, *Hafnia* (*H.*) *alvei* and *Staph. equorum*, plus the yeasts *D. hansenii*, *G. candidum* and *K. lactis*, several mutualistic interactions were observed [188]. *Lc. lactis* and the yeast *K. lactis*, the most active species on day one, enabled the rapid fermentation of lactose, and the lactate produced was rapidly consumed by the yeast species *D. hansenii* and *G. candidum*. The ensuing deacidification of the matrix by the yeasts allowed the ensuing development of all five acid-sensitive bacteria [189].

The biotic interactions between *D. hansenii* and strains of the acid-sensitive species *Brev. aurantiacum* and *H. alvei* have also been recently assessed in a mini-cheese model [190]. Transcriptomic profiling of the cheeses produced with different combinations of these three species revealed potential mechanisms of interaction involving iron acquisition, proteolysis, lipolysis, sulfur metabolism, and *D*-galactonate catabolism. Confirming the previous results by Dugat-Bony et al. [189], the growth of *D. hansenii* increased the pH, allowing for the development of *Brev. aurantiacum* and *H. alvei* [190]. Further, strong mutualistic interactions between the two bacteria were also observed. *Brev. aurantiacum* benefited from the production of siderophores by *H. alvei*, while *H. alvei* growth was

stimulated by sulfur amino acids and other energy compounds released from casein and triglycerides via the proteases and lipases secreted by *Brev. aurantiacum* [190]. Some of these interactions are of industrial interest since proteolysis increases the pool of methionine, the substrate for the formation of volatile sulfur compounds by *H. alvei*, which increase cheese flavor.

None of the above microbial interactions rules out others occurring [135,136]. Indeed, many and complex interactions between and within the different components of the cheese microbiota surely take place at the same time throughout manufacturing and ripening. For example, commensalistic and amensalistic interactions have been observed during the investigation of the interactions between the cheese microbes *Lc. lactis*, *Y. lipolytica*, and *Staph. xylosus* [191]. The numbers of *Y. lipolytica* were dramatically reduced by the presence of *Staph. xylosus*, whereas, although some changes in gene expression were observed, the growth of the lactic acid bacterium was not affected by the presence of either *Staph. xylosus* or *Y. lipolytica* [191]. Similarly, LAB and adventitious non-starter organisms may compete for citrate in cheese, while cooperation in terms of proteolysis and lipolysis may occur; all these interactions can lead to increased flavor formation [192–194]. Growth-detrimental interactions between *S. thermophilus* and *Lb. delbrueckii* subsp. *bulgaricus* in yogurt have also been reported. Strains of either species can produce bacteriocins that inhibit those of their partner [195,196].

6. Dynamics of Microbial Communities in Cheese

Microbial interactions determine the development, dynamics and activity of the microbial communities that compose the cheese microbiota, which may also influence cheese quality and safety [63,192,197,198]. Microbial communities often express emergent properties that cannot be predicted based on their individual members [199]. The robustness of microbiota may also be promoted by the taxonomic, genetic and functional redundancy seen in complex microbial communities [200]. To understand the causes and consequences of the microbial interactions affecting community dynamics and functionality, strategies are required that will help identify the patterns of microorganisms that determine the processes shaping the outcomes of the microbial interactions. These strategies must also assist in unraveling the molecular mechanisms underlying the interactions [201]. In this regard, the assistance of a vast array of state-of-the-art "omic" techniques is crucial [61,202]. For example, metagenomic surveys of the microbiota of cheeses [17,74,80,82,83,95,103,107,117,118,203–205] can help uncover patterns of community composition, while transcriptomic profiling [173,184,189–191,198,206] can be used to study microorganisms in a pairwise fashion and thus dissect interaction mechanisms. Besides, metabolomic techniques [115,116,207] can be used to identify the actual chemical mediators of these interactions [85,166,189,190,208,209]. The knowledge gathered through all these techniques may provide tools for managing and manipulating the microbiota and, consequently, can contribute to cheese quality and safety [210].

It has been consistently noted that the dominant microbial populations in different cheese varieties remain the same irrespective of whether the cheese is made from raw or pasteurized milk [42,102,103,211]. This suggests that cheese-specific environmental factors allow the consistent assembly of certain microbes in each particular cheese type [201,212]. Recently, the rind microbiota of a large set of cheeses with natural, smear, and bloomy rinds, although varied and complex, has been reported to be composed of easily tractable microbial communities [205]. Intensive sampling of cheeses from Europe and the USA made at different times of year has shown the assemblage of rind microbial communities to be very consistent. More importantly, in a simple *in vitro* system (10% cheese curd agar), Wolfe et al. [205] demonstrated that the different patterns of community composition and succession in cheese rinds can be easily reconstructed from a small pool of the commonest abundant taxa (seven bacteria and four fungal species) simply by changing the inoculum size and the rind washing and drying processes followed. Moisture was found to be the best predictor of the cheese rind community's composition. In bloomy rinds, the

numbers of *Galactomyces* and four genera of highly abundant *Proteobacteria* species were found to positively correlate with the moisture level [205], while molds, *Actinobacteria*, and *Staphylococcus* species, which are all abundant in dry, natural rinds, were negatively associated with this parameter. The same research group also showed that motile bacteria from rind microbial communities (*Serratia, Halomonas, Vibrio, Psychrobacter*, and others) use the humidity associated with the physical networks created by the co-occurring filamentous fungi for dispersal [208]. The latter study highlights how fungal-mediated bacterial dispersal can promote the growth of motile organisms over that of non-motile community members. In addition to shaping the composition of the cheese rind microbiota, this interaction could have quality and safety implications, depending on whether motile microbes are of technological relevance (*H. alvei, Psychrobacter* sp., etc.) or are pathogens (*L. monocytogenes*) [208].

By analyzing the spread of three closely related *Staphylococcus* species in cheese rind biofilms, it has been shown that biotic interactions can drive the patterns of microbial species distribution [209]. Surprisingly, based on growth and competition assays in the laboratory, *Staph. equorum* (the most abundant *Staphylococcus* in cheese) proved to be a slower colonizer and weaker competitor than *Staph. xylosus* and *Staph. saprophyticus* [208]. However, *Staph. equorum* was shown to be promoted by fungi, particularly by those of the genus *Scopulariopsis* [209]. Comparative genomic and transcriptomic experiments indicated that the potential mechanism underlying this bacterium–fungus interaction was based on iron utilization. Filamentous fungi release siderophores into the cheese matrix, and the bacterium responds by overexpressing siderophore-binding proteins [209]. This reaction provides *Staph. equorum* with an exclusive and inexpensive iron source.

Nine synthetic microbial communities consisting of different strains of three bacterial species (*Staph. equorum, Brev. aurantiacum*, and *Brachybacterium alimentarium*) have been reported to show different responses to abiotic (high salt) and biotic (the presence of the fungus *Penicillium*) disturbances [213]. Some combinations of strains showed no response, while others showed a substantial shift in community composition. These differing responses were shown to correlate with differences in pigment production (light yellow to orange) and with the volatile organic compounds emitted from the rinds (nutty to sulfury) [213]. This suggests that taxonomic profiling alone may not predict well the assembly, dynamics, and functions of cheese microbiomes. However, the results stress the importance of the microbial interactions in the flavor formation in the cheese rind. Chemicals triggering the assemblage of a community do not necessarily need to be physically close to the microbial responder. Indeed, volatile compounds produced by fungi have recently been found to stimulate the growth of *Vibrio casei* [214]. The latter study showed how volatile compounds may affect the development of a microbial community in cheese and demonstrated the feasibility of using airborne chemicals to control the composition (and thus activity) of the cheese microbiota.

Together, the above studies highlight how easily tractable microbial communities within the cheese microbiota can link the results of *in vitro* experiments with in situ observations [215]. Such associations might help determine the ecological processes contributing to species distribution and the abundance of microorganisms in cheese. A difficulty in inferring hypotheses regarding the relationships of ecological processes and microbial communities and in testing them experimentally is the inability to mirror accurately under laboratory settings the natural conditions encountered during cheese manufacturing and ripening [84,189,190,208,210]. However, understanding the mechanisms behind these interactions, and the environmental conditions that induce them, is a prerequisite for engineering communities for applied purposes [197,216]. The knowledge obtained in this regard might serve to support cheesemakers' empirical observations, such as that the use of fresh milk with low levels of psychrotrophs prevents the development of the spoilage fungus *Mucor* during ripening [217], and that lowering the humidity of the curd favors the growth of *G. candidum* while inhibiting that of *Mucor* [218]. An advantage might also be taken of biotic interactions between the typical members of the cheese microbiota to inhibit

the dynamics of cheese-borne pathogens such as *L. monocytogenes* and enteropathogenic *Escherichia coli* [219].

7. Microbiota-Based Starters

Despite the enormous advances made in resolving microbial safety hazards and spoilage issues, the dairy industry still faces important technological challenges beyond the phage infection, such as the need for improved science-based strategies to control cheese defects including the formation of splits associated with secondary fermentation [10,121,220], the appearance of calcium lactate crystals [122], and discolorations [84,120,221]. Reducing the presence of pathogens in raw milk-made cheeses [123,221], controlling spore-formers in cheeses made from pasteurized milk [11,13,138], and reducing the production and accumulation of biogenic amines in cheese [124] also need to be pursued. However, as has been repeatedly reported [207,222,223], the outcomes produced by the raw milk microbiota in cheeses during ripening cannot be reproduced by simply adding starter and ripening cultures. One solution for developing multipurpose functional starters would be to identify, isolate and characterize competitive microorganisms within dominant and key functional populations (the so-called "core microbiota") in each cheese type, and return them in a synthetic mixture for cheese manufacture and ripening [215,224].

Multi-species synthetic microbial communities are widely used in several biotechnological processes, as these may have properties that a single species or microbial strain alone could never show [225]. The main aim of a multi-species community culture is to occupy the ecosystem from a taxonomic viewpoint, but especially from a functional perspective [88,226]. This idea has proven successful in the inhibition of pathogens in plant roots, where, as shown above for the antilisterial activity of some cheese rind smears, the inhibition induced is deemed to be a property that emerges at the microbial community level [227]. The use of multispecies communities also shows promise for the treatment of intestinal disorders associated with microbial dysbiosis [228]; synthetic communities might soon be able to replace the unappealing treatments of fecal transplantation. To these ends, metagenomic data of the concerned ecosystem of interest can be examined by software tools [229] and in-network analyses [230,231] to search the samples for interactions between taxonomic units and biological samples. The relative abundance of biotypes, occurrence and exclusion patterns could also be scrutinized via correlation with the presence and concentration of key taste and aroma compounds [88,118]. Such analyses can help identify the core microbiota and key environmental factors that influence microbial colonization, development and activity. Using this strategy, Wang et al. [88] identified five genera as the core microbiota—*Lactobacillus, Saccharomyces, Pichia, Geotrichum*, and *Candida*—involved in the fermentation of a sorghum-derived liquor. Four yeast species (*Pichia kudriavzevii, G. candidum, Candida vini*, and *Sc. cerevisiae*) and one bacterium (*Lb. acetotolerans*) were then employed as representatives of each genus in experimental liquor manufacture. After fermentation, the synthetic mix was shown to have a flavor dynamics similar to that produced under standard conditions [88].

Synthetic microbial communities from cheese rinds containing various types of bacteria and fungi have already been used as smearing starters for the manufacture of smear-ripened cheeses [12,42,56,206]. Traditional smearing, in fact, involves an "old to young smearing" procedure, in which smears from mature cheeses dispersed in water or a saline solution are used to inoculate—as an undefined rind starter—the surface of young cheeses [39]. Some synthetic smear starters have been conceived [232] and typically contain three to six strains of deacidifying fungal species (usually *D. hansenii* and *G. candidum*) and acid-susceptible bacteria (*G. arilaitensis, Brev. aurantiacum, Brev. linens*, and/or *C. casei*). Occasionally, Gram-negative bacteria such as *H. alvei*, *Proteus vulgaris* or *Psychrobacter celer* can also be included, aiming at enhancing the production of volatile sulfur compounds [233,234]. At present, the design of such cultures is mostly empirical, and neither the biotic interactions between the different taxa involved nor the effects of abiotic factors are currently taken into account, which very commonly results in a colonization fail-

ure [145,235,236]. Scientifically sound, microbiota-based, multi-species starters composed of LAB and non-LAB species, and, if required, of eukaryotic organisms, would provide enzymatic activities that LAB alone do not possess, thus contributing to expanding the textural and flavor patterns of the cheeses produced with them. These starters might more easily resist the phage attack and reduce colonization by adventitious spoilage and pathogenic organisms.

8. Conclusions and Prospects

Abundant knowledge on the composition, diversity, and structure of the microbial communities in cheese has been accrued over recent decades via the use of HTS techniques. The diversity and number of species present within the microbial communities of different cheese varieties create the potential for a multitude of inter- and intra-species interactions, most of which, however, are currently unknown. Indeed, the interactions that have already been studied are limited to a few community members and a small number of exchanged metabolites. Even less is known about the molecular bases facilitating and regulating these exchanges. Neither do we have much knowledge regarding the conditions that allow the cheese microbiota to form and develop under the influence of biotic and abiotic factors, nor of how any of this translates into the improvement of cheese manufacture and ripening. As a consequence, successful cheese fermentations cannot be predicted, and technological failures of microbial origin are commonly inexplicable. In this regard, establishing chemical and/or microbial biomarkers to trace the milk fermentation would certainly be a valuable tool, which might contribute to enhancing cheese quality.

To get the most out of the omics revolution in cheesemaking, computational pipelines have to be developed to infer putative mechanisms of interaction between the many microbial populations. Constructing and using simple microbial communities in model systems might help unravel how microorganisms from complex consortia interact in their communities, and what influence they imprint on the sensorial properties of cheese. Confirmation is also required that the processes and mechanisms identified in model systems also work at the natural ecosystem scale, that is, at the cheese level. To that end, model communities should mimic natural populations as closely as possible; this will help throw light on the mechanisms involved in microbial colonization, functioning, and endurance of the different biotypes. Understanding microbial interactions of the biotypes with biotic and abiotic factors in cheese could help design strain mixtures as improved starter cultures. Knowledge of how microbes assemble into communities and the practical implications of these in cheesemaking could ultimately be used to improve the overall cheese quality and safety.

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