MICROORGANISMS AND ANIMALS: EXPLORING SYMBIOTIC RELATIONSHIPS IN BIOTECHNOLOGY

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Symbiosis is a close relationship between two biological species. This chapter explores the vital symbiotic relationships between animals and microorganisms, which are crucial for various physiological processes such as digestion, immunity and nutrient synthesis. Different forms of symbiosis, including mutualism, commensalism, and parasitism and their significance in biotechnology is described here. The importance of symbiosis in maintaining livestock health and productivity and its implications for biotechnology are highlighted. The chapter further explores diverse range of symbiotic relationships, including mutualistic relationships that benefit both parties, commensal relationships that benefit one party, and parasitic relationships that harm the host. Moreover, the mechanisms of formation and maintenance of these relationships and their impact on health and disease is discussed here. The importance of symbiotic relationships in developing antibiotic resistance and their potential in biotechnology is explored. Recent advances in synthetic biology have led to the development of advanced microbiome supporters and live biological therapeutics with improved assets. These products have the potential to revolutionize the field of biotechnology. Advances in transcriptomics, genome sequencing, and metagenomics have opened new avenues for studying symbiosis, enabling cross-species comparisons of bacterial evolution and host integration stages. These advances have also led to a better understanding of the mechanisms of symbiosis and its potential applications. Finally, the chapter explores future directions and emerging trends in symbiosis research, highlighting its potential for advancing livestock health and productivity.

1. Introduction

1.1. Definition and Types of Symbiosis

Symbiosis is defined as any close and long time biological relationship between two or more biological species (Wiesmann, Wang, Zhang, Liu, & Haney, 2023). Ruminant microorganisms and cattle have a symbiotic interaction. Microorganisms in the rumen help cattle digest plant cellulose. Microbes get home and nutrients, and cattle profit from the breakdown of complex plant components into absorbable nutrients, demonstrating mutualism. This connection is required for effective digestion in ruminants (X. Chen et al., 2022). Symbiotic relationships can be of various types such as

- **Mutualism:** If both organisms mutually benefit, it is called mutualism. This type of relationship can be seen in the rumen of cattle, where various microorganisms (bacteria, protozoa, and fungi) help digest cellulose from plant material. The microbes gain a habitat and nutrients, while the cattle benefit from the breakdown of complex plant materials converted to volatile fatty acids, that are used and absorbed for energy (Yang, Zhang, &

El-Mahallawy, 2024).

- **Commensalism:** If one organism is benefited and another organism is not harmed and benefited it is then called as commensalism. Cattle egrets frequently accompany animals, including cattle, buffalo, and horses. As these enormous creatures walk through grassy regions, they disrupt insects on the ground, making it simpler for egrets to catch and consume. The egrets benefit from having easy access to food without causing injury or serious damage to the animals they follow(Y. E. Chen, Fischbach, & Belkaid, 2018).
- **Parasitism:** When one organism is benefited and another organism is harmed it is known as parasitism(Ichihashi et al., 2020)Liver flukes are parasitic flatworms that infect the livers of animals including sheep, cattle, and goats. They induce liver tissue damages, resulting in lowered production, weight loss, and, in severe cases, it causes death. Livestock become sick after consuming water plants polluted with fluke larvae, showing a crucial parasitic link that affects livestock health and agriculture(Gunturu, Yegireddy, Mannem, Mekapogu, & Tollamadugu, 2019).

1.2. Importance of Symbiosis in Biotechnology

Symbiotic relationships are crucial in livestock farming, significantly enhancing animal health and productivity. These interactions, which include mutualistic, commensal, and sometimes parasitic relationships, are vital for nutrient absorption, disease resistance, and overall well-being. To break down complex plant elements like cellulose, ruminants like cows and sheep rely on a symbiotic connection with a wide variety of bacteria in their rumen. These microorganisms, comprising of fungi, bacteria, and protozoa ferment ingested food, converting it into volatile fatty acids, which serve as the primary energy source for the host. This mutualistic interaction enhances nutrient absorption efficiency and overall livestock productivity (Arshad et al., 2021).

Probiotic supplementation in livestock diets introduces beneficial bacteria that improve gut health, enhance digestion, and increase feed efficiency. This results in better growth rates, improved feed conversion ratios, and higher overall productivity (Bhogoju & Nahashon, 2022). Prebiotics, on the other hand, stimulate the maturation of beneficial gut bacteria, further promoting a healthy gut environment (Cangiano, Yohe, Steele, & Renaud, 2020). The presence of a balanced microbiota can help reduce stress in livestock by maintaining gut health and preventing dysbiosis (microbial imbalance). Reduced stress levels contribute to better animal welfare, which is closely linked to productivity and health (Ozbayram, Kleinsteuber, & Nikolausz, 2020).

1.3. Historical Perspective and Current Trends

The study of symbiotic relationships in livestock has a rich history. In the late 19th and early 20th centuries, scientists discovered the presence of microorganisms in the rumen of cattle and sheep, establishing the foundation for microbial ecology. Mid-20th century advancements, provided by Robert Hungate, allowed for culturing and understanding specific rumen bacteria (Pidcock, 2022). The modern era with molecular and genomic techniques, has fostered insights into microbial diversity and functions in livestock, enhancing our understanding of nutrient absorption and disease resistance (Ozbayram et al., 2020).

Recent and current modifications in research have been moved to practical applications of symbiotic relationship of livestock production. Probiotic and prebiotic supplements are being formulated to optimize gut health, enhance feed efficiency, and boost immunity in livestock (Ozbayram et al., 2020). Concurrently, research is investigating microbiota manipulation to ease methane emissions from ruminants, promoting more sustainable livestock farming practices (Hesham et al., 2021). These interventions aim to improve overall livestock productivity while addressing environmental impacts associated with animal agriculture

a. Emerging drug resistance is another challenge worldwide that is decreasing the efficacy of antibiotics in livestock, and it is a food chain that is polluting every single species. In this case, scientists are working on a symbiotic relationship between microbes and livestock which can enhance the productivity of livestock by overcoming antibiotic resistance in them. The symbiotic relationships concerns with bacteria and fungi can be an area that remains widely unknown for the discovery and development of new antibiotics (Gogineni, Chen, Hanna, Mayasari, & Hamann, 2020).

b. Synthetic biology and engineered symbioses, microbiome research, bio-remediation and bioenergy, co-culture systems are the recent trends in biotechnology (Lv et al., 2021).

c. The roles that microbiomes play in biotechnological applications are crucial for maintaining the health of humans, animals, plants, and the environment. Given microbiomes are found in a wide variety of natural and artificial environments, including those of people, plants, soils, sediments, and livestock animals.

d. Applications of microbiome, including various aspects such as biofertilizers, biocontrol agents, and pre- and probiotic food supplements are expected to provide valuable contributions to combat major societal challenges, such as zero hunger. They are being used to reverse biodiversity loss and global climate change (Bhogoju & Nahashon, 2022).

2. Microorganisms and Animals: An Overview

2.1. Microbial Diversity in Animal Hosts

The microbiome, which is an essential component of animal physiology and aids in the preservation of species, need to be enhanced and added to the database of future management techniques (Dallas & Warne, 2023). Any microbes that live in and on the host animal, including their genomes and extrachromosomal components, as well as their interactions with the skin, vaginal environment, and gastrointestinal tract (GIT), are collectively referred to as the "microbiota" (Xu et al., 2021). These two terms “microbiota” and “microbiome” are often used reciprocally. Organisms that have gut microbiota exist outside the mucosal layer and are essential for robust the host immunity and facilitating the link between the gut and brain (Xu et al., 2021). The GIT comprises the dense amount and largest diversity of microorganisms (Khan et al., 2023).

A community of commensal, symbiotic, and pathogenic microorganisms that live in the mammalian gut, such as bacteria, viruses, parasites, fungi, archaea, and protists, is referred to as the GIT microbiota (Jwher & Ezzulddin, 2022). Such kind of mammalian gastrointestinal tract is believed to have approximately 1014 bacteria consisting of 500–1000 unique species, which form a symbiotic relationship with the host. The microbiota that live on an organism are involved in digestion, the use of nutrients, the elimination of toxins, the fight against pathogens, also includes the modulation of the immunological and endocrine systems (Patil, Gooneratne, & Ju, 2020). There is a clear link between rumen bacteria and the digestion of cellulose and hemicellulose. A significant amount of research has been done on the fundamental laws guiding the cellulolytic bacteria *Butyrivibrio fibrisolvens* and *Ruminococcus flavefaciens*. The most prevalent bacterial families in the rumen were *Bacteroidales, Clostridiales, Butyrivibrio, Ruminococcus,* and *Prevotella* (X. Chen et al., 2022).

It is well known that microbiota is essential to the GIT of both ruminant and non-ruminant animals. Ruminal microbial organisms are essential to the nutrition and nutrient synthesis necessary for the growth and productivity of dairy animals (Gunturu et al., 2019). Animals and microorganisms have complex interactions that can be mutually beneficial (mutualism), neutral (commensalism), or even harmful (parasitism). Microbes act as a biological factor that regulates microbiota of the gastrointestinal tract coupled with the betterment of reaction with the environment and to make a strong impression of immunity response (Jwher & Ezzulddin, 2022).

Homo sapiens are vital symbiotic organisms. In GIT/gastrointestinal tract, bacteria constitute most of the microbial population. The Bacteroidaceae family contains at least 500 different species of bacteria, including *Clostridium, Lactobacillus, Eubacterium, Bifidobacterium,* and *Braceroids*. These bacterial species generally crossover with the GIT and exist amicably with the intestinal mucosa. The composition and abundance of this microbiota are determined by the physiological resources of the various GIT sections, and they are also influenced by a range of autogenous and allogeneic factors. Therefore, the microbial population supports cellular homeostasis, assists in nutritional utilization and digestion, and creates vitamins, enzymes, and other nutrients that are lacking in diets by acting as a protective barrier with antibacterial, antioxidant, and immunological characteristics (Melara et al., 2022).

In the United States, the deer tick *Ixodes scapularis*, is responsible to transmit an array of pathogens, including viruses like Powassan and the bacterium that causes Lyme borreliosis. It also carries the protozoan agent that causes babesiosis. But a variety of other microbes have also changed the symbiotic connections with this type of tick, and it seems likely that several of such microorganisms have developed methods to affect both their tick host and each other at the same time (Tsao, Hamer, Han, Sidge, & Hickling, 2021).

2.2. Types of Microbial Symbionts

Microbial symbionts' relationships with their hosts and each other can be compared to that of passengers sharing a ride. They may or may not interact directly; one may pay for the ride or the other may ride at another person's expense; they may be amicable, indifferent, or antagonistic; they may sit next to each other or keep apart to use different parts of the car; and they may exist in different places or remain there for an extended amount of time (Stewart & Bloom, 2020). Examples of these ride-sharing-like symbiotic connections, for instance, between microbiota and arthropods have been well-documented. Examples of beneficial interactions are the two bacterial endosymbionts of the glassy-winged sharpshooter (Homalodisca coagulata), which synthesize different essential metabolites for the host and possibly for each other, and the gut commensal bacteria of an Aedes aegypti mosquito that promotes arboviral infection by altering the gut epithelial layer (Wu et al., 2019). An example of a symbiotic interaction in arthropods includes the inhibition of Plasmodium falciparum growth within the midgut of Anopheles gambiae mosquitos resulting from the initiation of reactive oxygen species produced by an endogenous Enterobacter strain.

Presumably, a multitude of symbiotic protozoa are hosted by most metazoa. These symbionts reside in the gut lumen, on ciliated epithelia like the exoskeletons of crustaceans and the gills of aquatic creatures, and on body surfaces. Some of them also exist extracellular or intracellular, in different tissues and organs. On the other hand, it is likely that symbionts are descended from free-living species that changed to live in the unique environments that animals make up, and these evolutionary processes are currently occurring. As a result, it is difficult to distinguish between symbiotic and free-living protozoa. Several organisms from the genera Acanthamoeba and Naegleria are well-known examples. These species are freshwater amoebae that live freely. However, isolated cells may occasionally infect people, resulting in deadly diseases (Visvesvara et al. 2007).

It is commonly known that the pig gut microbiota is crucial for maintaining metabolic homeostasis and for carrying out several other physiological, neurological, and immune processes, including pathogen defense and the digestion of food that pig would not otherwise be able to digest. The hallmark of optimal health is a diverse gut microbial ecology or balanced microbiota; nevertheless, alterations in the composition of microbes, both in terms of quantity and quality, can lead to the emergence of a wide range of illnesses. On the other hand, conditions brought on by stress or other variables have been demonstrated to damage the microbiome (Patil et al., 2020). The main prokaryotic symbiont of I. scapularis is Rickettsia buchneri, which has a different relationship to the tick than B. burgdorferi. It seems to be an obligatory intracellular bacterium that may colonize a variety of organs, such as the ovaries, midgut tissues, and salivary glands (Stewart & Bloom,

2020). The difference between eukaryotic and prokaryotic symbionts is described here in Table 1.

Table :1 Difference between eukaryotic and prokaryotic symbionts(Skipper, 2005)

Properties	Eukaryotic symbionts	Prokaryotic symbionts
Cell structure	Complex cell structure with membrane-bound organelles	Simple cell structure without membrane-bound organelles
Genetic material	DNA enclosed within a nucleus	DNA is free-floating within the cell, not enclosed in a nucleus
Size	Generally larger (10-100 micrometers)	Generally smaller (1-5 micrometers)
Reproduction	Sexual and asexual reproduction through mitosis and meiosis	Asexual reproduction through binary fission
Examples	Protozoa in the rumen of cattle that aid in breaking down complex carbohydrates	Gut bacteria (e.g., Lactobacillus species) that assist in nutrient absorption and pathogen resistance, Rumen bacteria (e.g., Fibrobacter succinogenes, Ruminococcus albus) that help in cellulose digestion.

3. Diversity of symbiotic Relationship

When organisms from two distinct species coexist for a considerable amount of time, this is known as symbiosis (Hom & Penn, 2021). Symbionts are the organisms that participate in symbiosis. Microbial symbiosis refers to the various forms of symbiosis in which a microbe is involved e.g., mutualism, commensalism etc. (Wiesmann et al., 2023) . Numerous animals that are thought to be nonpathogenic exhibit microbial symbiosis, and plenty of bacteria have evolved to live and colonize in biological systems (Hom & Penn, 2021).

3.1. Mutualistic symbionts

Animal fluids, cells, surfaces, cavities, and notably their guts are home to a wide variety of microorganisms, in which at least 15% to 20% of all insects have symbiotic relationships with bacteria (Hom & Penn, 2021). The bacterial Symbionts have emerged throughout the last ten years. The efficiency and health of ruminants is influenced by the mutualistic relationship between the microorganisms living in their gastrointestinal tracts (GITs) and the host (Schluter & Foster, 2012). The immune system of the host and the GIT microbiota interact to affect not just the GIT but also other tracts in the body. Microorganisms perform various functions in detoxifying harmful substances present in feed, thereby lowering the risk of toxin-related diseases in livestock (Xu et al., 2021).

a) Commensal symbionts

The commensal microbiota improves animal health in several ways, including by aiding in the digestion of plant fiber that would normally be indigestible. Besides that, it supplies the host with building blocks such as carbohydrates, peptides, and lipids, plus minerals and energy sources like volatile fatty acids. It also modifies the immune system by producing cytokines and antibodies (Sanjorjo, Tseten, Kang, Kwon, & Kim, 2023). Pathogens and immune cells are physically separated by the microbiota, which also competes with them for resources and adhesion sites (Leijon, Atkins, Waller, & Artursson, 2021). Furthermore, these microorganisms stop the growth of harmful substances by generating antimicrobial agents. It includes organic acids, hydrogen peroxide, bacteriocins, and biosurfactants (Yang et al., 2024).

Throughout these organs, the distribution changes according to the factors associated with the host and unique physiochemical characteristics of the colonization site, ruminants, like cattle, sheep, and goats, depend on their gut flora for proper digestion and nutritional absorption as well as general health (Xu et al., 2021). The rumen, the main stomach chamber in ruminants, is home to

these microorganisms, which are mostly bacteria, archaea, protozoa, and fungus as summarized in Table 2 (Sanjorjo et al., 2023). They aid in the digestion of complex plant elements like cellulose and hemicellulose, which the animals are unable to digest on their own (X. Chen et al., 2022).

A case study in which one of the important cellulolytic bacterium found in the rumen of many ruminants is Fibrobacter succinogenes (Fakih et al., 2023). One of the main components of cell walls in plants, cellulose, is broken down by this bacterium into simpler sugars that the host can ingest and use as fuel. This relationship is a prime example of commensal symbiosis, in which the ruminant gains in better nutrient absorption and fiber digestion, and the bacteria benefits from a consistent environment and supply of nutrients. Research shows that F. succinogenes colonizes the rumen after birth, establishing a stable population that resides in animals for a lifetime. It produces cellulolytic enzymes that efficiently degrade cellulose into fermentable sugar (Al-Shawi et al., 2020). The significance of this commensal connection is demonstrated by the improved growth rates and conversion of feed efficiency of ruminants with a healthy population of F. succinogenes (Swift et al., 2021).

b) Parasitic symbionts

A relationship in which one organism, the parasite, benefits at the burden of the other, the host, is known as a parasitic symbiosis. Because it depends on the host for resources like nutrition, the parasite frequently causes varying degrees of damage to the host (Ichihashi et al., 2020). For example, ticks on mammals feeding on their blood such as deer dogs and humans, fleas fees on human blood and cause allergic reactions. They can be the source of various diseases e.g., Lime disease parasitic symbionts include plasmodium in humans causing malaria, liver flukes in sheep and cattle. Numerous pathogenic microorganisms can cause diarrhea, viruses (such as bovine viral diarrhea and ovine rota-virus), bacteria (for instance Salmonella enteritidis and E. coli K99/O157), and parasites such as Cryptosporidium sp. and Coccidium sp. (Tsao et al., 2021). Slow weight increase in sheep and beef cattle due to respiratory diseases can result in significant financial losses for producers of lamb and beef (Yang et al., 2024).

Table:2 Composition of rumen gut microbiota (Jwher & Ezzulddin, 2022; Sanjorjo et al., 2023)

Type of Microbiota	Examples
Bacteria	*Fibrobacter succinogenes, Ruminococcus flavefacien, Ruminococcus albus, Butyrivibrio fibrisolvens,Prevotella ruminicola Bacteroides, Methanobrevibacter ruminantium, Selenomonas ruminantium*
Archea	*Methanobrevibacter ruminantium, Methanosarcina barkeri, Methanobacterium formicicum, Methanomicrobium mobile*
Protozoa	*Entodinium, Epidinium, Diplodinium, Isotricha*
Fungi	*Neocallimastix frontalis, priomyces, Orpinomyces, Anaeromyces*

Body cavities, epidermis mucosa, respiratory, gastrointestinal, and urogenital tracts are all colonized by microbial populations as shown in the cattle microbiome (Hobson & Stewart, 1988). Throughout these organs, the distribution changes according to the host factors and unique characteristics of the colonization site of different animals such as ruminants, like cattle, sheep, and goats, depend on their gut flora for proper digestion and nutritional absorption as well as general health (Xu et al., 2021). They help in the digestion of complex plant elements like cellulose and hemicellulose, which the animals are unable to digest on their own (X. Chen et al., 2022).

4. Habitat and Transmission of Microorganisms within Animals

4.1. Environmental and Host Factors Influencing Microbial Colonization

An imbalance in the microbiome, known as dysbiosis, is marked by a disruption in the balance of microorganisms, leading to a decrease in diversity, an overgrowth of harmful pathogens, a decline

in beneficial commensals, and changes in metabolic function. This imbalance is directly linked to the progression of chronic inflammatory and metabolic diseases, as well as an enhance risk of infections (Frank et al., 2007; Turnbaugh et al., 2006). Difference in the composition of various microorganisms between and within host species is caused by multiple factors that can be lifestyle, age, geography nutrition, and life events (such as antibiotic treatments and stress) (Cammack, Austin, Lamberson, Conant, & Cunningham, 2018; Spor, Koren, & Ley, 2011; Taschuk & Griebel, 2012).

Host phylogeny significantly influences microbiome composition, with trends in core microbiota largely restricted to specific host phylogenetic clades (Ley et al., 2008). While some animals rely on endosymbionts for survival, others have minimal evidence of a core microbiome (D Ainsworth et al., 2015). Most animals fall in between, with a core microbiome that provides benefits but is shaped by dietary variation, social groups, and environmental exposures, leading to inter-individual microbiome variation within a species (R. K. Singh et al., 2017).

Host genetics significantly influence the microbiome composition, influencing host characteristics like immunology, metabolism, and morphology. Understanding host genes and metabolic pathways helps understand physiological processes and evolutionary forces acting on the host and microbiome (Ryu & Davenport, 2022). Because different microbial species have been a greater part of metabolic enzymes encoded in their genomes, enabling them to metabolize varied substrates to support growth, diet plays a major role among these parameters (Scott, Gratz, Sheridan, Flint, & Duncan, 2013). Seasonal variations in diet or other environmental stressors (drought, habitat fragmentation, etc.) might modify the taxonomic composition of the gut microbiota or the expression of metabolic genes within the same species. Certain Bacteroides members, for instance, can change the production of enzymes that break down carbohydrates based on the availability of complicated plant-derived substrates as opposed to endogenous host substrates like mucins (McNulty et al., 2013). The exposed living environment, including temperature, humidity, location, and herd management, significantly influences the symbiotic relationship of rumen microbiota and host (K. Liu et al., 2021). Changes in host living conditions cause microbial genomes in the gastrointestinal tract to shift, affecting the gut microbiomes of different hosts (K. Liu et al., 2021).

4.2. Vertical and Horizontal Transmission Mechanisms

Research on the different microbiomes has surged for the last 15 years, driven by growing interest in its link to health and disease, and technological advancements. The impact of collaborative efforts like the Human Microbiome Project and Earth Microbiome Project have further accelerated this field of study (Ghosh & Pramanik, 2021; Gilbert, Jansson, & Knight, 2014). Unlike animals and plants, which pass on their genomes to their offspring through a standard and well-understood process, microbiomes are inherited and shared through various unconventional methods, including both vertical (from parent to offspring) and horizontal (between individuals) transmission pathways (Rosenberg & Zilber-Rosenberg, 2021). Horizontal transmission originates from the environment, while vertical transmission involves the migration of microbiota from parent to child without interacting with environmental bacteria (Rosenberg & Zilber-Rosenberg, 2021).

Although horizontal gene transfer is difficult to classify as an ecological interaction, it may be advantageous to both parties and fall under the umbrella of cooperation. The well-known instance is when antibiotics are used in a medium containing multiple microbial taxa, and most bacteria are first sensitive to a substance they have never encountered before. Antibiotic-resistant mutants will spread widely. Lastly, susceptible cells from the same taxon or from a different taxon may receive the DNA fragment that confers antibiotic resistance (Moënne-Loccoz, Mavingui, Combes, Normand, & Steinberg, 2015).

Pregnancy, nursing, and birthing all include the critical process of microbe transmission from mother to child. The mother's gut microorganisms are extremely important in determining how the offspring's immunity and metabolic functions develop (S. Liu, Zhang, & Ma, 2023). During

pregnancy, the mother's gut microbes change and prepare for vertical transmission, and short chain consisting of fatty acids produced by these microbes promotes the growth and development of the neonatal immune system (S. Liu et al., 2023). After birth, the mother's microbes transmit to the baby through breast milk, influencing the development of their immune system. Immune cells and blood flow mediate the microorganisms' migration from the gut of the mother to the baby and mammary gland, enabling the beneficial flora to be passed on to the future generation as described in Figure 1 (S. Liu et al., 2023). This process is essential for the maturation of the offspring's immune system and has a long-term impact on their health and disease susceptibility (S. Liu et al., 2023)

4.3. Role of Animal Behavior in Microbial Dispersal

Animals' bacterial communities can be influenced by their social structure and behavior, either through shared habitats or direct physical contact. The genetic composition of the microbiota may change because of these social processes, which may have an impact on the services that microbiomes offer to their hosts. The microbiome can influence host social behavior. Microbial communities can convey a great deal of information about animals because of their metabolism, which can release volatile compounds that are detectable by animals, and because bacterial communities can change depending on the characteristics of their hosts. Their hosts may even appropriate this function for social signaling. Additionally, microorganisms have the unique characteristic to actively "hack" the host nervous system to enhance microbial transmission, essentially altering host behavior for their fitness.

Microbes spread socially through grooming, feeding, mouth-to-mouth interactions, and coprophagy, offering health benefits to hosts. Gut bacteria from social interactions reduce honeybee vulnerability to parasites like *Lotmaria passim* and *Crithidia bombi* while solitary bees lack these gut microbes causing more severe impacts.

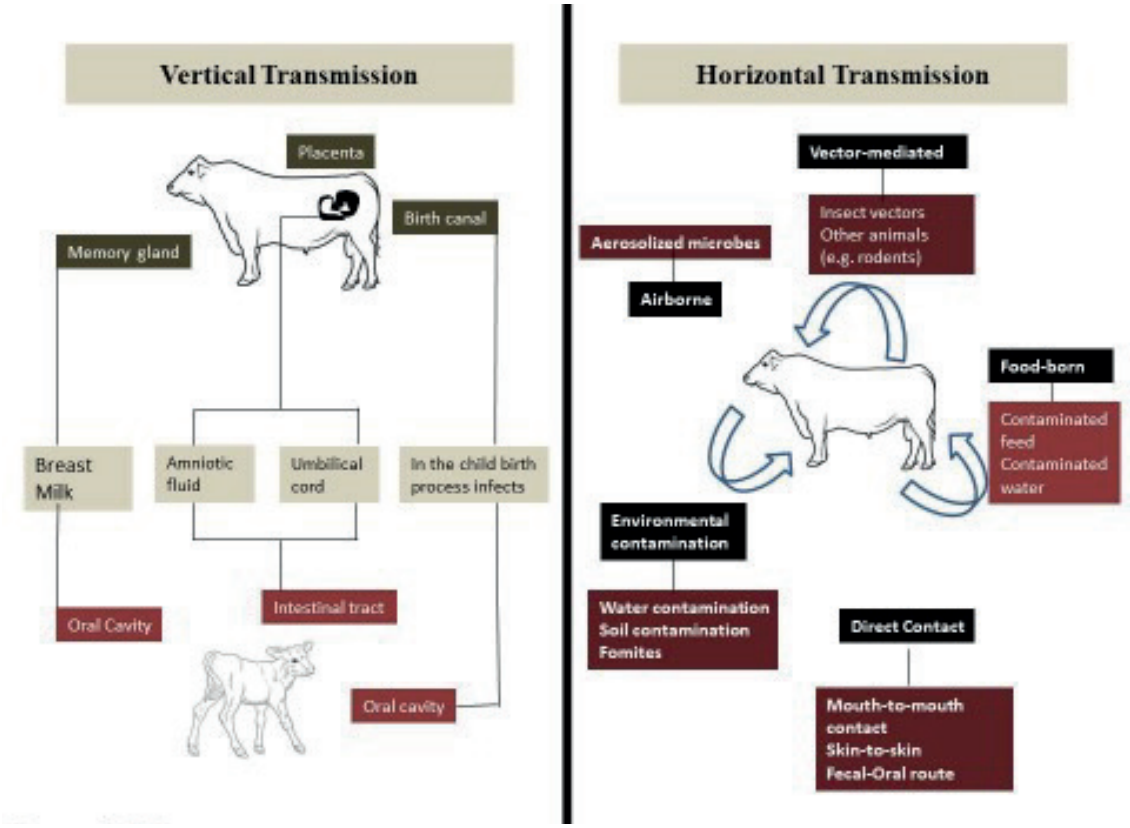


Figure 1; Diagram showing pathways of microbial transmission (vertical and horizontal) in livestock. On the left side in figure vertical transmission modes are given. On the right side horizontal transmission modes are given. Microbial transmission in livestock v in vertical transmission happens via placenta, memory glands & birth canal while in horizontal transmission transfer can be from aerosolized, vector mediated, food borne, environmental contamination and can be via direct contact.

5. Role of Microbe-Animal Symbiosis in Health and Disease

5.1. Disease Tolerance and Immune Modulation:

The formation of the gastrointestinal tract (GIT) microbial community is essential for activating and regulating a calf's immune system in its early life stages (Gomez, Galvão, Rodriguez-Lecompte, & Costa, 2019). Previous studies have indicated that the hindgut is vital for immune system development in animals with single-chambered stomachs (Mulder et al., 2011). Current research shows that the microbial population that resides in the hindgut portion of animal gut, is equally important for the proper development of a calf's immune system (Malmuthuge & Guan, 2017), and this immune system imposes an impact on GIT health of calf by affecting digestion and energy production. The immune system engages with the microbiota via the immunoregulatory pathway, that impact the production of cytokines and cytokinetic reactions as well as prostaglandin E2 (Feng, Chen, & Wang, 2018). These interactions subsequently influence brain function (Das & Ranjan, 2020). The main role of the microbiota-gut-brain-axis (MGBA) in the modulation of host health has been extensively studied in humans as well as in animals. This bidirectional conversation can be influenced by infections in the gastrointestinal tract (GIT) microbiota, which can negatively impact the brain function and increase sickness behavior in animals, or by a healthy GIT microbiota, which can enhance brain function. Germ free animals studies reveals a significant factor about inclusion of probiotics and prebiotics leads to behavioral changes (Kraimi et al., 2019).

Livestock production often involves unavoidable stressors like weaning and transportation. Studies have shown that transportation stress increase level of some pro-inflammatory cytokines, hormones including adrenocorticotropic (ACTH) and cortisol (Li et al., 2019). Additionally, an abundance of ruminal Lactobacillus has been found to correlate positively with interleukins (IL-6 and IL-4). The addition of prebiotics and probiotics in ruminant diets can help prevent HPA axis signaling, which reduces anxiety. Research on dairy calves indicates that before weaning, a multispecies probiotic supplement improves growth, decreases diarrheal occurrence, changes the fecal microbiota (raising Bifidobacterium, Lactobacillus, Collinsella, and Saccharomyces), and lowers serum IgA, IgG, and IgM concentrations (Y. Wu et al., 2021). Overall, the GIT microbiota significantly affects animal behavior and health by directly influencing the immune system (Han et al., 2017).

5.2. Detoxification and Metabolic Cooperation:

It has been demonstrated that microbes possessing certain metabolic capacities can exist in the natural world. It is probable that bacteria that degrade toxins eaten by herbivores are widespread among herbivorous species (Hammer & Bowers, 2015). Strong selection pressure for breakdown capacity should be applied to microorganisms in high toxin abundance local habitats, such as those around toxin-producing plants (Stapleton, Kohl, & Dearing, 2022). Moreover, because of horizontal gene transfer and quick generation rates, detoxifying capacity should proliferate quickly among microbial communities. Additionally, microbes have the benefit of catalyzing a wide variety of reactions that are not yet understood in herbivores including vertebrates and invertebrates. Examples of these reactions include those catalyzed by isothiocyanate hydrolase and catechol dioxygenases (Wadke, Kandasamy, Vogel, & Lah, 2016). Furthermore, microorganisms generate laccases, which are incapable of carrying out phenolic detoxification in animals while vertebrate herbivores lack these enzymes (De Fine Licht et al., 2013).

5.3. Microbiome Dysbiosis and Disease Development:

Disturbances in the delicate equilibrium of the microbiological consortium during ailment instances triggers dysbiosis, which can result in the emergence or disappearance of distinct microbial species (Wilkins, Monga, & Miller, 2019). Dysbiosis can cause or worsen various disease phenotypes in cattle, such as Johne's disease, uterine infections, and metabolic disorders like ruminant acidosis (Derakhshani et al., 2016; Jeon et al., 2016).

When intramammary infections occur, mastitis is characterized by an inflammatory reaction that compromises the physical barrier of the mammary glands (Abebe, Hatiya, Abera, Megersa, & Asmare, 2016). It is categorized into clinical and subclinical forms based on disease severity. Subclinical mastitis has no symptoms despite the presence of infections, whereas clinical mastitis exhibits noticeable alterations in the milk and udder (A. Ashraf & Imran, 2018). Usually, a variety of bacterial species are the etiological agents of mastitis. Major pathogens include *Mycoplasma sp., Escherichia coli, Streptococcus dysgalactiae, Staphylococcus aureus,* and *Streptococcus agalactiae.* The coagulase-negative *Staphylococci* and *Corynebacterium* species are examples of minor pathogens (Dalanezi et al., 2020). Persistent diarrhea is a hallmark of Johne's illness, which causes emaciation, malnutrition, and large financial losses for the global livestock business (Rathnaiah et al., 2017). The non-motile, slow-growing mycobacteria known as Mycobacterium avium subsp. Johne's sickness is due to paratuberculosis (MAP) (Britton, Cassidy, O'Donovan, Gordon, & Markey, 2016).

6. Dynamics of Microbe-Animal Symbiosis in Antibiotic Resistance

6.1. Evolution of Antibiotic Resistance in Symbiotic Microorganisms:

Livestock gastrointestinal environments frequently include low and sublethal amounts of antibiotics, which promote the formation of ARGs and help avoid sickness. Merely 5–15% of studies on antibiotic-resistant genes published between 2000 and 2020 explored the role that cattle may play in potential hazards, even though livestock utilizes over half of all antibiotics used worldwide. As of 2020, the proportion of relevant research on livestock out of all published articles on antibiotic resistance is still less than 17%, despite an increase in this area. Thus, to lessen the risk of antibiotic resistance, funding for this kind of study is required. The prolonged use of antibiotic to encourage animal development and prevent diseases may be the reason for the higher content of residual antibiotics in livestock farmyard waste when compared to human waste (Sim et al., 2011). As a result, microorganisms on animal farms are under more pressure to evolve resistance genes through natural selection. Layer and sow dung had higher levels of ARG pollution than chicken and piglet/fattening pig manure, respectively, however the ARG level in chicken manure appeared to be higher in virtually all kinds of poultry and livestock farms than in pig and cow farms (Qian et al., 2018).

Tetracycline and sulfa resistance genes were measured in terms of number and variety in chicken manure from small- and medium-sized chicken farms in Hangzhou, Eastern China by Cheng et al. (Cheng, Chen, Su, & Yan, 2013). The results showed that the relative abundance of various ARGs in the feces of medium-sized chicken farms was higher than that of small chicken farms. Moreover, tetQ exhibited the highest relative abundance in these farms, followed by tetM and sul2. According to a study, hatcheries were common place for blaOXA-1, blaMOX-like, blaCIT-like, blaSHV, and blaFOX (Osman et al., 2018). Antibiotics containing tetracycline are frequently used to treat illnesses and also encourage growth in pig farms (Q. Q. Zhang, Ying, Pan, Liu, & Zhao, 2015). As a result, pig feces frequently include tetracycline resistance genes, with the genes that safeguard ribosomal proteins being the most common.

6.2. Impact of Antibiotic Use on Livestock Microbiomes:

Shortly after the extensive use of antibiotics as growth promoters in cattle in the 1950s, there have been multiple cases of drug-resistant pathogen-related outbreaks in humans and farm animals worldwide (Datta, 1962). Antibiotic-resistant microorganism infections now cause large healthcare and financial losses, as well as longer hospital admissions, higher death rates, and an increased risk of complications (Carmeli, Troillet, Karchmer, & Samore, 1999; Cosgrove, Kaye, Eliopoulous, & Carmeli, 2002; Lautenbach, Patel, Bilker, Edelstein, & Fishman, 2001). Antibiotics that do not have adequate safety profiles must be used to treat infections brought on by resistant bacteria. For

example, colistin, an antibiotic of last resort, can successfully treat infections caused by highly resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*; however, patients who take it suffer from severe renal failure and deterioration (Levin et al., 1999). The discovery in 2016 of plasmid-mediated resistance to colistin in Escherichia coli isolates isolated from pigs raises even more concerns over the possibility that the drug's therapeutic benefits may be short-lived (Y. Y. Liu et al., 2016). If all of our prescription antibiotics are eventually rendered ineffective by resistant bacteria, humanity will return to the pre-antibiotic era, when even little cuts can become infected and have fatal consequences (Ventola, 2015).

6.3.Strategies to Mitigate Antibiotic Resistance:

The numbers of *Campylobacter* jejuni in broiler chicks were consistently reduced in experiments employing bacteriophage treatments in vivo (Carvalho et al., 2010; Loc Carrillo et al., 2005). According to Chinivasagam and colleagues, phage cocktails were used to manage *Campylobacter* in broiler chickens at the farm. The bacteriophage mixtures were chosen using *E. coli* and *C. jejuni* as their targets. Before the birds were killed, the phages were given orally to 47-day-old birds for a whole day. The market-ready broilers' levels of *Campylobacter* were shown to be effectively reduced by the phage cocktails, according to the study the authors recommended extending the therapy for more than 24 hours to ensure continued phage replication for the biocontrol of *Campylobacter* in vivo, nevertheless, because some of the birds in farm B had low phage titres (Chinivasagam et al., 2020). Animal feeds have traditionally included probiotics, prebiotics, and synbiotics to promote the expansion of aquaculture and animal husbandry (Tan, Chan, Lee, & Goh, 2016).

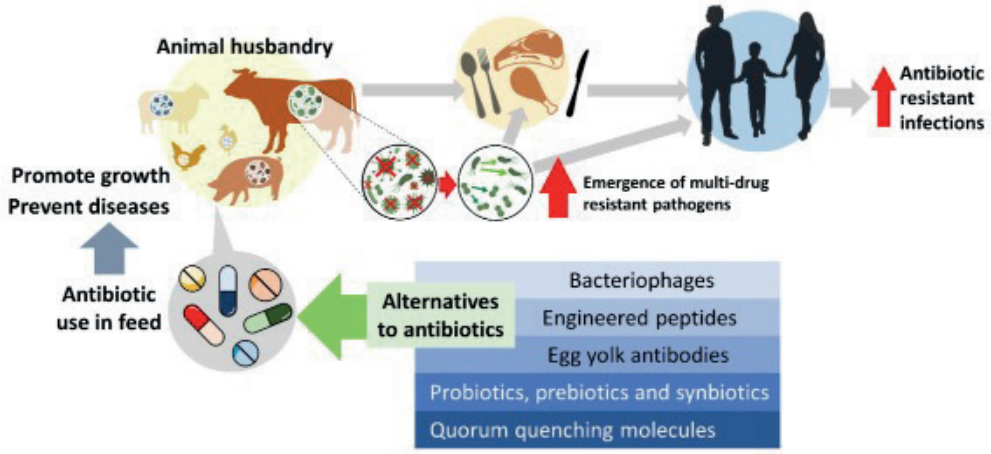


Figure 2. Process of antibiotic resistance development in microbial communities of livestock

7. Biotechnological Applications of Microbe-Animal Symbiosis

7.1. Probiotics and Animal Health:

The use of probiotics in animals has increased since the mid-1970s (Fuller, 2012). Probiotic supplements have been administered to farm animals as therapeutic supplements to lower morbidity and mortality, enhance feeding behavior, and boost yields of meat, milk, and eggs yield (Kabir, Rahman, Rahman, Rahman, & Ahmed, 2004; Naglaa, 2013; Rai, Yadav, & Lakhani, 2013). Probiotics have been shown to have the ability to limit the growth of undesirable microbes through at least two different mechanisms direct cell-to-cell contacts and/or the creation of inhibitory chemicals (Jonkers, 2016). According to Chaucheyras-Durand and Durand (2010), probiotics produce compounds known as organic acids, hydrogen peroxide, bacteriocins, and biosurfactants, which are antimicrobials and can inhibit the growth of pathogenic bacteria. Lactic and acetic acids are the most often produced compounds by probiotic bacteria; they lower pH and prevent the growth of infections. Additionally, probiotics strengthen immunity against intestinal infections by competitively colonizing intestinal adhesion sites and nutrients (Boirivant & Strober, 2007; Parvez, Malik, Ah Kang, & Kim, 2006).

Probiotics are thought to upregulate the expression of toll-like receptors (TLRs), which is one complex way in which they stimulate the innate immune system. Tumor necrosis factor-α (TNF-α), interleukin-4 (IL-4), and interferon-γ (IFN-γ) are among the cytokines that are released as a result ((R. Ashraf & Shah, 2014). According to Casas and Dobrogosz (2000); Ezema (2013) it has been shown that taking probiotics increases illness resistance and reduces metabolic stress and mortality. A basic diet supplemented with a probiotic blend containing *Lactobacillus casei, Lactobacillus acidophilus, Bifidobacterium thermophiles,* and *Enterococcus faecium* increased the content of immunoglobulins (Ig) M and G in turkeys. This enhanced the illness resistance and growth efficiency of the turkeys (ÇEtïn, Güçlü, & Cetin, 2005).

7.2. Microbial Bioremediation and Environmental Applications:

The use of microorganisms for example bacteria to enhance the environment is known as bioremediation, which goes beyond probiotics. Additionally, garbage and other hazardous pollutants are neutralized, detoxified, removed, cleaned up, broken down, and/or decomposed into less toxic or non-toxic chemicals using microorganisms in the bioremediation process. In an aquaculture setting, microorganisms have easy access to the digestive tracts of the animals and come into close touch with them through their gills and food supply.

Probiotics can be applied in two different ways directly to food (combined into the diet formulation) or indirectly to the environment (mixed with water and/or sediment). The first method involves adding probiotics, which are beneficial microbes, and decomposers to the feed. These additives work to improve feed quality by changing the feed's constituents into forms that are easier for the intestines to absorb, which increases feed digestibility. The ecology around the second application will be better since it will break down harmful substances like ammonia, sulfur, fish excrement, and surplus feed that could attract pathogens and other undesirable micro- and macroflora.

Meanwhile, adding compost to the soil is one approach to enhance its environmental quality and it also introduces bacteria to the soil. Using a starter or microbes to speed up the organic material's beneficial decomposition for plants is a more efficient way to create compost. Applying compost to agricultural land has two advantages it increases the amount of organic matter in the soil and improves the microbial biota of the soil. Effectively employing microbes to enhance agriculture, animal husbandry, and fisheries requires the development of tailored microbial cocktails for each specific type of plant, animal, or fish (Kompiang, 2009).

7.3. Agricultural Innovations: Enhancing Animal Productivity:

Animal breeding primarily focuses on the genetic development of economically important qualities such as meat output, meat quality, and illness resistance. The CRISPR/Cas system is a fantastic resource for animal biotechnology research and cattle production. It has transformed the field of genetic manipulation and dramatically expanded its applicability. Along with base editing and gene editing, post-transcriptional engineering using CRISPR/Cas system-based technologies and transcriptional control have advanced quickly, prime editing and transcriptional regulation (Gaj, 2021; Kantor, McClements, & MacLaren, 2020).

One of the most important applications of genome editing is to increase the resistance in farm animals against diseases. In addition to causing the animal husbandry industry to incur significant financial losses, infectious illnesses in farm animals also present a risk to human health producing anti-foot-and-mouth disease virus (FMDV) shRNA through the breeding of antiviral animals, such as pigs and cattle devoid of prion protein has been successfully accomplished through the use of transgenic and gene targeting techniques (Hu et al., 2015; Richt et al., 2007). Recently, the efficiency of raising animals resistant to disease has greatly increased thanks to genome editing technology, when the leukotoxin from *Mannheimia haemolytica* interacts with the uncleaved signal peptide of CD18 protein, ruminant leukocytes are cytolyzed causing acute severe lung tissue damage and acute inflammation, which causes a significant financial loss for the global cow sector (Shanthalingam

& Srikumaran, 2009). Zinc finger nuclease (ZFNs), a protein used in first-generation gene editing technology, has been used to create a single amino acid mutation in the bovine CD18 protein (Shanthalingam et al., 2016). Cattle with the CD18 gene altered had leukocytes that expressed CD18 protein without the signal peptide; as a result, the leukocytes were immune to the cytolysis caused by leukotoxin.

8. Techniques for Studying Animal-Microbe Symbiosis

8.1. Omics Technologies: Metagenomics, Metatranscriptomics and Metaproteomics:

The microbial communities (microbiota) that exist in the gastrointestinal tract (GIT) of cattle are being studied using state-of-the-art omics technologies instead of traditional cultivation methods and pure culture characterization. Culture-independent molecular techniques are widely used because of the discrepancy between in situ and cultivable diversity. The 16S ribosomal RNA gene-based techniques for microbial community profiling have grown as tools for describing microbial communities and the relationships amongst the microbes inhabiting the gastrointestinal tract. Shotgun pyrosequencing of the cDNA and total DNA yields metagenomic or metatranscriptomic data, respectively. The reads need to be quality filtered, contig assembled, binned, and allocated to potential gene functions and taxonomy. Metaproteomic studies investigate a sample's protein inventory at a particular moment in time. This makes it possible to identify the metabolic pathways expressed by the active microbial fraction. To obtain a pure protein sample and prevent the co-extraction of eukaryotic proteins, the first crucial step is to identify an optimal sample preparation strategy. The technological equipment that is available determines the workflow that follows.

8.2. In vivo and In vitro Models:

Scientists studying symbiosis are resorting to model systems. Fortunately, a number of potent models that were crucial for understanding developmental biology have also been used to research host-microbe interactions, such as hydra, the fruit fly, worm, and mouse (Bosch, 2013; Burns & Guillemin, 2017; Charroux & Royet, 2012; Clavel, Lagkouvardos, Blaut, & Stecher, 2016; Davis, Bryda, Gillespie, & Ericsson, 2016; Douglas, 2018; Klimovich & Bosch, 2018; Martino, Ma, & Leulier, 2017; Schulenburg & Félix, 2017; Shapira, 2017; Stagaman, Burns, Guillemin, & Bohannan, 2017; F. Zhang et al., 2017; Zhu et al., 2016).

Nematostella vectensis, the starlet sea anemone, is a good model for understanding the mechanisms driving dynamic colonization processes throughout host development because of the distinct microbiota it has for each of its three developmental life phases (Har et al., 2015; Mortzfeld et al., 2016).The ontogenetic core signature of N. vectensis´ was preserved despite significant changes in the microbiological composition caused by environmental fluctuations. Moreover, analysis of the bacterial communities of N. vectensis polyps from five different populations revealed a strong correlation between host biogeography and bacterial diversity, despite years of laboratory culturing (Mortzfeld et al., 2016).

Without being constrained by ethical considerations, in vitro fermentative models are thought to be excellent tools for screening a wide range of substances, including pathogens, medications, toxic or radioactive compounds, and ingredients in food, to determine how they affect and are affected by microbial populations and gastrointestinal environments. More complex continuous in vitro models include one or more connected, pH-controlled chemostats that simulate different parts of the human colon and are infected with fecal bacteria (Venema & Van den Abbeele, 2013). Batch incubations using anaerobic conditions and dense fecal microbiota are another type of in vitro model.

Fermenters are usually inoculated with liquid fecal suspension obtained from a single individual or from a combination of feces from several subjects. In the last example, fecal samples are used to inoculate a fed-batch fermenter, producing a standardized inoculum that is frozen for storage. A

method for immobilizing fecal microbiota in mixed xanthan-gellan gum gel beads was created by to maintain microbial variety and reach high cell densities throughout lengthy, continuous colonic fermentations. The model was recently improved to create PolyFermS, enabling the development of complex intestinal ecosystems in several reactors in a stable and repeatable manner (Cinquin, Le Blay, Fliss, & Lacroix, 2004). This makes it possible to compare the impacts of different treatments to a control reactor and examine their effects in parallel (Zihler Berner et al., 2013).

Because of its transparent body that makes it possible to visualize microbial infection and colonization, and its genetic tractability, Caenorhabditis elegans has become a valuable model for studying host-microbe interactions. Furthermore, there are morphological and functional similarities between the intestinal cells of C. elegans and other animals, such as vertebrates (Brenner, 1974). The bacteria that inhabit the intestinal lumen spontaneously make up the C. elegans gut microbiome. Feeding fluorescently tagged C. elegans bacteria and watching for fluorescence in the lumen is a typical way to see the presence of bacteria in the intestine. However, research has demonstrated that fluorescence is unable to differentiate living, intact bacteria from dead ones, with GFP-expressing E. coli OP50-1 demonstrating TEM revealed no intact bacteria, although there was fluorescence in the gut lumen (Hsiao, Chen, Yang, & Ho, 2013). When fluorescently tagged transgenic bacteria are used in trials to explore the microbiome colonization of the C. elegans gut, this disparity might cause confusion and possibly lead to inaccurate findings about the ability of bacteria to develop a niche and proliferate in the gut lumen.

Confocal laser scanning microscopy (CLSM) is one of the methods that is utilized often (Pawley, 2006). Fungi, plants, and other plant-like creatures have deep relationships and complex structural relationships with their substrates. In the heyday of their existence, CLSM emerged as a common tool for analyses of their interactions with microorganisms.

With CLSM, three different categories of objects can be identified (1) genetically modified organisms (GMOs) producing fluorescent proteins; (2) autofluorescent substrates, cells, and tissues; and (3) cells, tissues, and molecules stained with one or more fluorochromes. Since autofluorescent signals on biological and synthetic substrates are usually viewed as a negative aspect of CLSM images, efforts are often undertaken to prevent them (Lo Piccolo et al., 2010).

8.3. Bioinformatics and Computational Approaches:

With CLSM, three different categories of objects can be identified (1) genetically modified organisms (GMOs) producing fluorescent proteins; (2) autofluorescent substrates, cells, and tissues; and (3) cells, tissues, and molecules stained with one or more fluorochromes. Autofluorescence of synthetic and biological substrates is usually viewed as a negative. A plethora of bioinformatic tools have been developed and are extensively employed in the processing of metagenomic and amplicon sequence data. Researchers can now perform integrated metagenomic analyses and visualize results without command-line operations or strong computational knowledge thanks to web servers like MG-RAST (Meyer et al., 2008), IMG/M (Markowitz et al., 2014), EBI Metagenomics (Hunter et al., 2014), and SILVAngs (Quast et al., 2013), as well as pipelines like MEGAN (Schloss et al., 2009), QIIME (H. M. Chen & Lifschitz, 1989), and Mothur (Schloss et al., 2009).

By dividing reads into distinct species using particular sequence features found in a metagenomic dataset, composition-based methods enhance the efficiency of de novo metagenomic assembly. For instance, bin sequences based on the composition and coverages of tetra-nucleotide frequencies, such as MaxBin (Y. W. Wu, Tang, Tringe, Simmons, & Singer, 2014), metaBAT (Kang, Froula, Egan, & Wang, 2015), and CONCOCT (Alneberg et al., 2014).

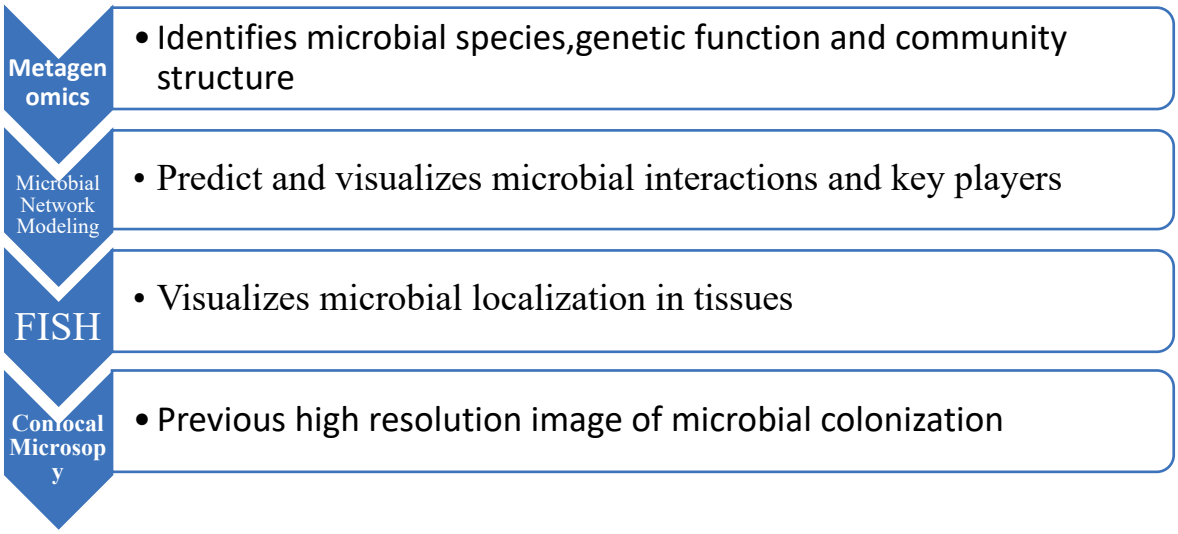


Figure 3. Schematic showing various techniques and their applications in studying symbiosis in livestock.

9. Genomic Insights into Prokaryote–Animal Symbioses

Due to the ecological ubiquity of bacteria, it is common to discover a number of prokaryotic species interacting closely with members of different eukaryotic taxa, frequently resulting in the long-lasting partnership known as symbiosis (Moya, Peretó, Gil, & Latorre, 2008). The link between the host and symbiont in the majority of prokaryotic and eukaryotic symbioses is so intimate that the microorganisms cannot be cultivated, making them challenging to research (Moya et al., 2008). Advances in transcriptomics, genome sequencing, and metagenomics have opened new avenues for studying symbiosis, enabling cross-species comparisons of bacterial evolution and host integration stages (J. P. McCutcheon & Moran, 2007; Shigenobu, Watanabe, Hattori, Sakaki, & Ishikawa, 2000).

9.1. Comparative Genomics of Host and Symbionts:

Symbionts genome;

The genomes of intracellular etiologic and protocooperative bacteria are smaller and include more AT (J. J. J. N. R. G. Wernegreen, 2002). Reductive-genome evolution occurs due to population dynamics and new environment requirements. Many genes are eliminated, while others become redundant, promoting genetic drift and allowing accumulation due to natural selection (Itoh, Martin, & Nei, 2002; N. A. J. P. o. t. N. A. o. S. Moran, 1996; Moya et al., 2008). These factors work together to advance the range of genes that can vanished and decrease the likelihood of the hereditary interchange through crossing over. These genes include those that are involved in genetic material healing and recombination, which can be advantageous but are not essential (Moya et al., 2008). Despite their small size, the smallest bacterial genomes prioritize genes essential for basic cellular processes like transcription, translation, and replication. Surprisingly, the only other consistently preserved genes are those involved in protein folding and stability, specifically Hsp70 molecular chaperone complex. These microscopic creatures' survival and ability to function depend heavily on these enzymes (J. P. J. C. o. i. m. McCutcheon, 2010).

Endosymbiont genomes have smaller, higher AT contents, likely due to DNA repair loss and mutational bias towards AT, affecting protein structure and function, impacting numerous genes (J. J. J. C. o. i. g. Wernegreen & development, 2005). The size reduction and AT content increase in endosymbionts vary based on the age of the association, with younger associations having smaller genomes and higher AT content (Baumann, 2005; Dale, Maudlin, & Microbiology, 1999; Moya, Latorre, Sabater-Muñoz, & Silva, 2002).

After transitioning to an obligate symbiosis, there was a massive loss of genes (10-20% retention) (Dale & Moran, 2006) likely due to large deletions and chromosomal rearrangements facilitated by mobile elements like insertion sequences (N. A. Moran & Mira, 2001). These mobile elements were abundant in recently acquired endosymbionts but were later removed as they became detrimental, leading to genome degradation and streamlining in older associations (N. A. Moran, Plague, & development, 2004; Plague, Dunbar, Tran, & Moran, 2008). When a genome shrinks, it's mainly because genes are being lost over time, spread out across the genome. This happens in a specific pattern a gene becomes inactive due to small changes, then gets shorter and shorter until it's completely gone (Gómez-Valero, Silva, Simon, & Latorre, 2007; Silva, Latorre, & Moya, 2001). The main reason for genome shrinkage is gene downsizing due to deletion or mutation, not just their shortening (Pérez-Brocal et al., 2006).

It is implied by host specialization that the host is now reliant on the bacterium for survival and procreation. The host's adaptive alterations comprise the creation of focused cells where microbes live, functional mechanisms for regulating microbial inhabitants, and adjustments to its immune system to combat the invader cells (Moya et al., 2008).

9.2. Genomic Adaptations in Symbiotic Relationships:

The hologenome theory of evolution suggests that genetic variation in symbiotic microbiota or host can be caused by microbial amplification, novel strain acquisition, and horizontal gene transfer, while host genome variation during sexual reproduction and development promotes symbiotic interaction.

Larger endosymbiont genomes preserve genes involved in multiple metabolic pathways, while smaller genomes have most disappeared. Endosymbionts have limited transport capacities, despite conserved pathways for nutrient production (Ren & Paulsen, 2005). Cellulolytic microorganisms are crucial for livestock animal nutrition, with their early emergence in newborn ruminants indicating quick development and fiber utilization (Jami, Israel, Kotser, & Mizrahi, 2013; Moraïs & Mizrahi, 2019). Ruminal cellulolysis is primarily attributed to protists, fungi, and bacteria, but their specific roles remain a topic of debate (Delfosse-Debusscher, Thines-Sempoux, Vanbelle, & Latteur, 1979; Lee, Ha, Cheng, & microbiology, 2000). Because LAB and yeasts (S. cerevisiae) can influence the subtleties of microbial community in the rumen and the process by which dietary factors degrade and utilized as probiotics and ruminal activators (Doyle et al., 2019; Mohammed, Mahmood, & Abas, 2018). In order to identify microbial membrane patterns such as peptidoglycan via receptors, hosts have built molecular systems (Moya et al., 2008). Microbial sensors are evolutionary pathogen recognition receptors crucial for defense against invasive microbes. Probiotic strains may modify TLR expression to exert their defense against infections (Akira, Uematsu, & Takeuchi, 2006).

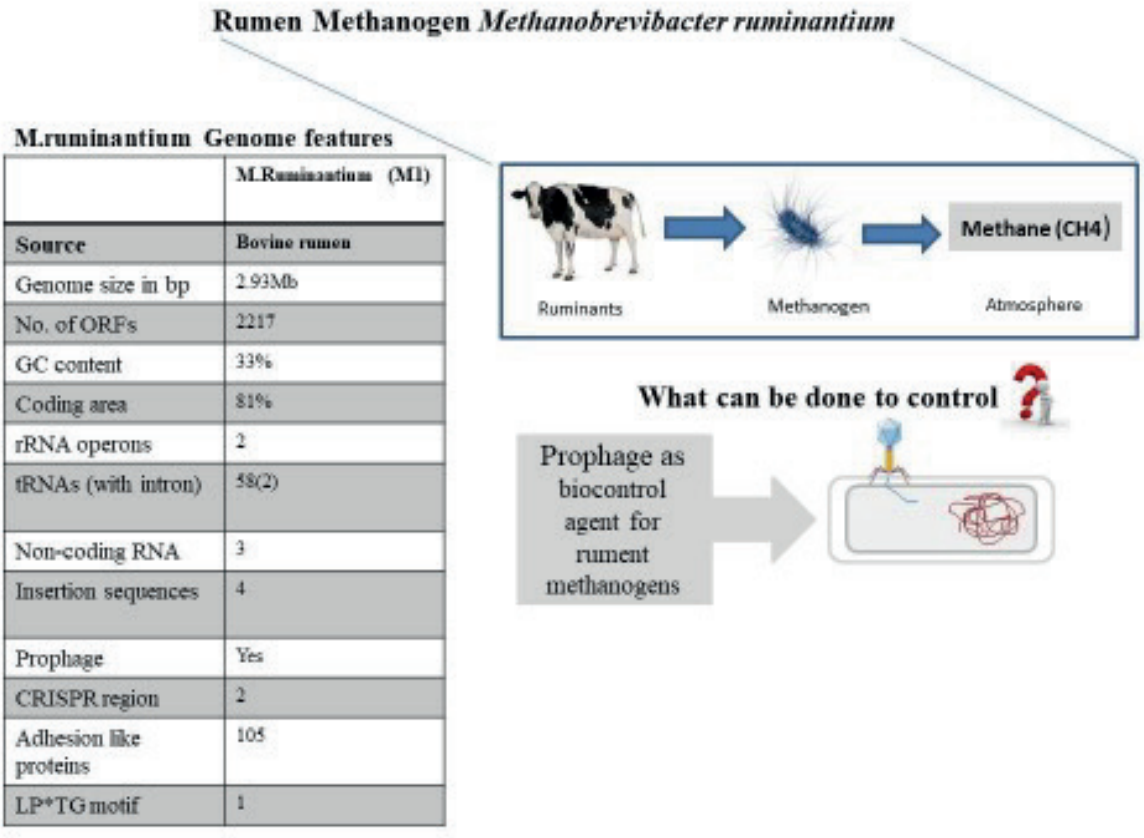
10. Applications in Synthetic Biology and Genetic Engineering:

It has been shown in recent years that these vast microbiomes and diversified microbiota have a tremendous impact on the life of both plants and animals.

10.1 Designing genetically modified probiotics

Nutritional supplements featuring active microbial entities that settle and reshape the enteric microbiota are known as probiotics (Dowarah, Verma, & Agarwal, 2017). Scientists first concentrated on using probiotics for treating and preventing abdominal infections brought on by specific bacterial strains that could replace unhealthy bacteria in the gut and stop the development of hazardous germs (Salas-Jara, Ilabaca, Vega, & García, 2016). Advanced probiotics (APs) and microbial-based therapeutic agents (MBTAs) with enhanced characteristics such as those engineered through precision microbiology have gained significant attention in the industry (T. P. Singh & Natraj, 2021; Steidler & gastroenterology, 2003).

Probiotics can affect the host in several ways, such as altering the enteric microbiota, regulating the defense system, and producing beneficial compounds. This enhances the host's defenses and promotes a balanced relationship between the host and microorganisms (Mugwanda et al., 2023). These peptides are essential for the immune system's stimulation, pathogen-killing, gut microbiota maintenance, and defense against harmful microbes (Mandal, Silva, & Franco, 2014). Additionally, probiotics aid in the digestion of fiber in cattle and lipids in humans. Certain probiotic strains have the capacity to activate certain facets of native protection (Alvarez-Olmos & Oberhelman, 2001; Torres-Sanchez et al., 2022). Genetic engineering has been used to enhance the health benefits of NGPs, targeting various illnesses and health problems in humans and animals (Abouelela & Helmy, 2024; T. P. Singh & Natraj, 2021). For example *Saccharomyces boulardii* and *cerevisiae*, two types of yeast, have been found to have probiotic properties in farm animals, altering the balance of gut bacteria, lowering the likelihood of microbial imbalance and generating essential nutrients and biological catalysts (Garcia-Mazcorro et al., 2020; Latorre et al., 2015; Ugwuoke, Okwesili, Dim, Okonkwo, & Ndofor-Foleng, 2021). Two beneficial bacteria, *Lactobacillus salivarius* and *Pediococcus parvulus*, found in the gastrointestinal tract of poultry, have shown to be resistant to harsh conditions like acidic environments, high salt concentrations, and bile salts. Moreover, they have been found to settle the spread of harmful germs like Salmonella, *E. coli*, and *Campylobacter* in laboratory tests (Menconi et al., 2014).



	M.Ruminantium (M1)
Source	**Bovine rumen**
Genome size in bp	2.93Mb
No. of ORFs	2217
GC content	33%
Coding area	81%
rRNA operons	2
tRNAs (with intron)	58(2)
Non-coding RNA	3
Insertion sequences	4
Prophage	Yes
CRISPR region	2
Adhesion like proteins	105
LP*TG motif	1

Figure 4. Genome comparison between a livestock host and its symbiont (Rumen Methogen Methanobrevibacter ruminantium); Ruman harbors methanogenic archea. Methane (a greenhouse gas) in ruminants is produced through the activity of methanogenic archaea, such as Methanobrevibacter ruminantium, which shows main role in ruminal methanogenesis process. Phage have been proposed as biocontrol agents for rumen methanogens and have main ecological impact on bacterial communities in the rumen (Hegarty & Klieve, 1999). The genomic sequence provides new insight

of this methanogen and helps for developing therapeutic interventions for methane mitigation

11. Innovative Perspectives on Pathogenic Relationships

11.1. Molecular Mechanisms of Pathogenesis

The term pathogenicity describes the potential of a pathogen to infect and inflict harm on host, making it a pathogen (Van Baarlen, Van Belkum, Summerbell, Crous, & Thomma, 2007). The host-pathogen interaction is like a lock and key, requiring a precise genetic match to enable colonization or infection. The genetic compatibility of both parties determines the outcome, with genetic variation, mutant selection, and interaction progression influencing the dynamics of this complex relationship (Lynch & Conery, 2003). Microbes and hosts can form relationships like parasitism, commensalism, or mutualistic symbiosis, with delicate balance. Disruptions can cause mutualists or commensals to become pathogenic, or introduce pathogenic bacteria to new hosts (Tanaka, Christensen, Takemoto, Park, & Scott, 2006). Animals sense helpful commensal microbes through receptors, which are crucial for preserving the host's health (Villena, Kitazawa, Van Wees, Pieterse, & Takahashi, 2018).

When a harmful pathogen enters the body, it triggers a rapid response from the immune system's "first line of defense" cells like stromal and epithelial cells, which act like sensors to detect and alert the body to potential threats (Matzinger, 2007). These ancient defense mechanisms, found in all animals and plants, help distinguish between harmless and harmful substances, and initiate a response to protect the body (Fontana & Vance, 2011; Glass, 2012). Bodies have an early warning system that detects harmful pathogens, like bacteria and viruses, through special receptors called Pattern Recognition Receptors (PRRs) (Kersse, Bertrand, Lamkanfi, & Vandenabeele, 2011). These receptors recognize specific patterns on pathogens that are different from our own cells and trigger an immune response to fight the infection. This early detection system is present in many cell types, including immune cells and cells lining our bodily surfaces (Kumar, Kawai, & Akira, 2011). Particularly most familiar PRRs are called toll-alike Receptors, and small changes in their sequence can affect how they respond to different pathogens (Werling, Jann, Offord, Glass, & Coffey, 2009). There are many other types of PRRs, including those that detect genetic material like RNA and DNA.

Damaged cells release "danger signals" that trigger an inflammatory response, alerting the immune system to potential threats (Glass, 2012). These signals, also known as "alarmins", are detected by specific receptors, including some that also detect pathogens (Manson, Thiemermann, & Brohi, 2012). Once pathogens enter the body, they trigger a cascade of signals that alert the immune system (Glass, 2012). This leads to a coordinated response, involving various signaling cascades and gene regulators, which ultimately activates production of particles that fight inflammation and infection, such as cytokines. If the immune response is strong and rapid, it can effectively clear the infection and prevent disease (Bianchi, 2007). The defense system has two essential arms natural and specific. The natural response happens quickly and triggers the adaptive response, which takes longer to develop. The adaptive response involves cells called T & B lymphocytes, which synergize to fight infection (Hill, 2012). There are different types of T cells, such as Th1 and Th2, which have different roles in fighting infection and regulating the immune response (Ouyang, Rutz, Crellin, Valdez, & Hymowitz, 2011). Macrophages, a type of immune cell, can also have different roles, such as pro-inflammatory and anti-inflammatory macrophages, which are involved in fighting infection as well as regulating the immune response (Mills, Kincaid, Alt, Heilman, & Hill, 2000). Understanding how these cells work together and how they are influenced by genetics can help us develop new ways to improve immune function and resistance to disease in animals (Calenge, Kaiser, Vignal, & Beaumont, 2010; Glass, 2012).

For example, Salmonella is an opportunistic cytosolic microbe that infects phagocytic or non-phagocytic cells and reproduces there. It uses protein export machines (injectosome system)

and enters enterocytes and accessory cells in the intestine. Salmonella enters macrophages through phagocytosis, injects effector proteins, and travels to lymph nodes, liver, spleen, and lymphoid follicles (Ibarra & Steele-Mortimer, 2009). Host immune cells recognize Salmonella through conserved pathogenic molecular patterns (CPMPs) and host cell-derived danger signals (HCDDS), stimulating an immune defense response. This recognition is modulated by innate immune sensors (IISs) and pattern-recognition receptors (PRRs), which activate downstream signaling pathways, including NF-κB and triggering the production of immune-activating cytokines, to combat the invasive microorganism (Crawford et al., 2010; Kobayashi et al., 2002).

11.2. Host-Pathogen Interaction Studies

Our knowledge for control of animal protection systems against pathogens and their interactions with beneficial microorganisms has significantly improved because of the post-genomic era's technological advancements. Animal-microbe associations can so now be researched more quickly and thoroughly than ever before. Two of the main practical advantages of probiotic ingestion are immune activation and an even gut microbiota (Hammes & Hertel, 2002; Parracho, McCartney, & Gibson, 2007; Salminen & Isolauri, 2006).

Enterocin-producing Enterococci have been shown to promote health in food animals (poultry and rabbits) by fighting off harmful bacteria like Salmonella, Staphylococci, and others (A Lauková, Guba, Nemcová, & Mareková, 2004; Andrea Lauková et al., 2006; Simonová et al., 2009). These beneficial bacteria produce enterocins, which work in various ways to provide antimicrobial activity (Guillermo et al., 2015). For example, Enterococcus faecium (EF 55) has been found to increase the number of lymphocytes and boost the immune system in poultry infected with Salmonella (Levkut et al., 2012).

The pathogenic E. Coli, which can cause severe disease in humans, is often carried and shed by cattle (Guillermo et al., 2015). However, research has shown that a specific probiotic blend containing Lactobacillus gallinarum and Streptococcus bovis, derived from cattle rumen, can significantly decrease enterohemorrhagic E. Coli excretion in infected calves. This reduction is associated with an increase in gut-derived fatty acids (Ohya, AKIBA, & ITO, 2001), indicating a positive impact on the animal's digestive health (Guillermo et al., 2015).

11.3. Novel Approaches to Controlling Pathogenic Microbes

The world is currently faced with the formidable task of increasing crop and livestock productivity without resorting to the careless use of antibiotics (Reid, 2011). A whole new field of study has emerged as a result of the promise of microbiota-based treatments for treating Salmonella infections (De Jong, Parry, van der Poll, & Wiersinga, 2012). Beneficial microorganisms, used as biocontrol agents, offer a promising solution to manage plant diseases by outcompeting pathogens or directly combating them through the production of antimicrobial compounds, thereby protecting plants from harm (Mansfield, 2000). By adding specific beneficial fungus like *Tricoderma harzianum* and *Gloicocadium virens* to organic mulch, "bioenhanced mulches" were produced that successfully inhibited the growth of a dangerous disease (*P. cinnamomi*) in avocado roots. When crop disease burden is modest, using beneficial microorganisms as biocontrol agents is a safe and efficient way to manage crops (Costa, Menge, & Casale, 2000). The research of microbiome interactions among various farm animal groups is part of Customized Combination of Microbial-Based Therapies (CCMBT), which aims to identify the most effective combinations for disease control and promoting animal health (Peixoto, Harkins, & Nelson, 2021).

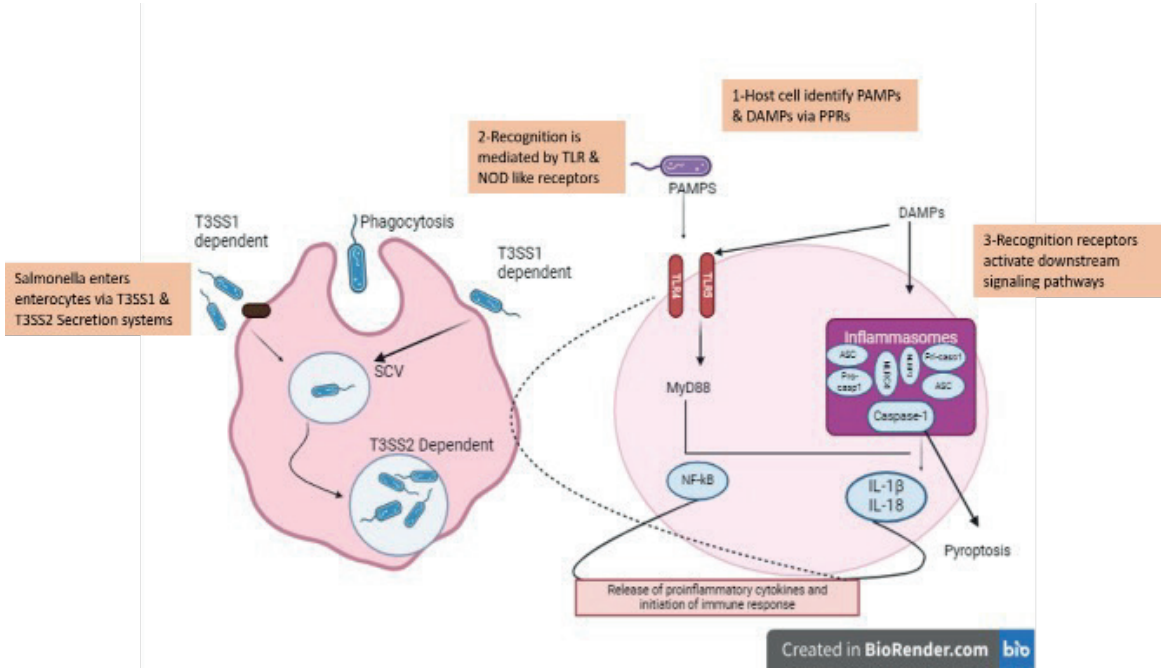


Figure 5. Host-Pathogen Interaction; Host immune cells recognize Salmonella through pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), triggering an immune response. This recognition is mediated by microbial sensors, which activate downstream signaling pathways, including Inflammatory response, to combat the infection. On the other side, salmonella enters the cell via 3 mechanisms a) T3SS1 dependent b) T3SS2 dependent c) phagocytosis.

12. Future Directions and Emerging Trends

12.1. Prospects for New Symbiosis-Based Technologies

Antibiotic resistance genes are being transferred by pathogens, leading to multidrug resistance. Scientists suggest using beneficial microorganisms to modify plant and animal immune systems as a viable substitute for antimicrobials (Jones, Vance, & Dangl, 2016). Current probiotics are modified using gene editing technologies ZFNs, TALEN, CRISPR, CRISPR-Cas and CRISPR-Cas 9, ensuring their effectiveness in fighting pathogen infections and controlling beneficial interactions (Ma et al., 2022). Probiotics that have been engineered utilized to treat numerous illnesses and health problems in humans & animals (Abouelela & Helmy, 2024). Host-pathogen systems biology has various applications and is expected to play a crucial role in personalized medicine, with ultimate goal of creating individualized digital models to simulate and predict disease progression and treatment outcomes (Forst, 2010).

Molecular biology boosts animal production (Peixoto et al., 2021). We have now entered an era where the scientific community has access to vast amounts of genomic data, ranging from traditional sequencing to pacific biosciences & portable sequencing as well as second generation sequencing and genome analyzers (Peixoto et al., 2021). Thanks to sequencing, analysis, and comparison, metagenomic technologies have increased our understanding of rumen microbiomes and revealed a wide universe of previously undiscovered microbial species (Peixoto et al., 2021). To better understand ruminant greenhouse gas emissions, recent research have used meta-omics methodologies (Peixoto et al., 2021). The goal of the Hungate 1000 project (Wallace et al., 2019) is to create a reference set of rumen microorganisms and sequence the genomes of rumen microbes (Seshadri et al., 2018). The Global Rumen Census measures the variety of microbes in rumen samples from different farming environments and geographical areas. The Rumen Microbial Genomics (RMG) Network includes these initiatives. There are now 501 genomic sequences in the database.

A different study discovered a core microbiome connected to host genetics and phenotype, and concluded that the rumen microbiome is heritable (Andersen, Kunath, Hagen, Arntzen, & Pope, 2021; Denman, Morgavi, & McSweeney, 2018). The research of microbiome interactions among various farm animal groups is part of Customized Combination of Microbial-Based Therapies (CCMBT), which aims to identify the most effective combinations for disease control and promoting animal health (Peixoto et al., 2021).

12.2. Challenges and Opportunities in Biotechnology

Despite the progress made in developing probiotics for use in commercial poultry, more commercially beneficial microorganisms that are feed-durable, economically viable and storage stable are desperately needed to boost adoption and compliance. The production of NGPs is fraught with difficulties. Some of these are the Selection and characterization of suitable probiotic strains (Stanton et al., 2003); Probiotic survival during storage and gastrointestinal transit (Soccol et al., 2014); Commercial probiotic production (Foligné, Daniel, & Pot, 2013); Probiotic stability and shelf life (Ranjan et al., 2022); There is an pressing need for advanced microbial cultivation techniques, cost-effective genetic and metagenetic analysis, robust bioengineering tools for precision editing and modification of microbial genetic material (Abouelela & Helmy, 2024); The conclusion of biocompatibility testing; and safety and efficacious trials in humans (O'Toole, Marchesi, & Hill, 2017); The application of genetically engineered microbes in next-generation products (NGPs) presents further regulatory compliance challenges & public perception hurdles (Abouelela & Helmy, 2024).

To overcome these difficulties in biotechnology, we should encourage the improvement of novel, particular transport methods, including inclusion or micro inclusion, to safeguard probiotic strains throughout storage and gastrointestinal transit (Abouelela & Helmy, 2024). Refining artifact stability, steadiness, and quality switch can be achieved through optimizing manufacturing processes (Abouelela & Helmy, 2024).

12.3. Future Research Directions and Emerging Fields

Researchers are working to pinpoint the precise bacterial strains that will help everyone the most through methods such as metagenomic sequencing. Advanced delivery technologies, such as time-release formulations and nanoparticles, are being developed to guarantee tailored administration to enteric zones or enterocytes, maintaining exposure to beneficial bacteria. With biotechnological advancements emerging fields work for microbiome associated benefits. Recent literature explores various strategies for creating probiotics, including heterologous protein expression, incorporating foreign enzymes, and metabolic engineering. These strategies allow for the use of complex byproducts of DNA technology, modified lipopolysaccharides, and detoxification through novel metabolic pathways (Steidler & gastroenterology, 2003). Neutralizing antibodies from recombinant bacteria can now be produced thanks to the development of single chain (ScFv) antibody technology (Steidler & gastroenterology, 2003).

A novel strategy for avoiding microbial illnesses is replacement treatment (Steidler & gastroenterology, 2003). A synthetic genome was successfully inserted into a Mycoplasma cell envelope, demonstrating groundbreaking artificial genome technology, resulting in a simple, fully functional artificial cell (Cordova, Hoeltgebaum, Machado, & SANTOS, 2016). Genome transplantation in Mycoplasma species allows comparative genomics studies, identifying crucial proteins and functional capabilities, despite being limited to unusual bacteria like Mollicutes (Karas et al., 2019). Research is now being conducted to create a novel, affordable, feed-stable probiotic that is clinically beneficial for both human and animal use, has a broad range of applications, and is easy to administer. Products containing Bacillus spores should reduce *Salmonella* as effectively as possible as well as be comparable to the antibiotic bacitracin in terms of preventing necrotic enteritis in both experimental and commercial field testing (Guillermo et al., 2015); engage closely

with the microbiota or host cells to maximize any potential probiotic effects (Guillermo et al., 2015); lessen pathogens that are transmitted through food (Aureli, Fiore, Scalfaro, Casale, & Franciosa, 2010); Avoid certain gastrointestinal conditions (Guillermo et al., 2015); Colon carcinogenesis can be prevented by either live vegetative cells or endospores from certain isolates (Park, Jeon, Park, Paik, & Bulletin, 2007); release antibiotic agents against bacteria that are Gram-positive, including *Clostridium difficile, E. faecium,* and *Staphylococcus aureus* (O'mahony et al., 2001); and the present objective is to create an innovative probiotic that is clinically successful for both human and animal use, has a simple administration system, and is widely utilized. In both experimental and commercial field trials, that isolate of Bacillus subtilis spores is as effective for reducing *Salmonella* as FloraMaxTM, and is comparable to the antibiotic bacitracin for preventing necrotic enteritis (Shivaramaiah et al., 2011; Wolfenden et al., 2010).

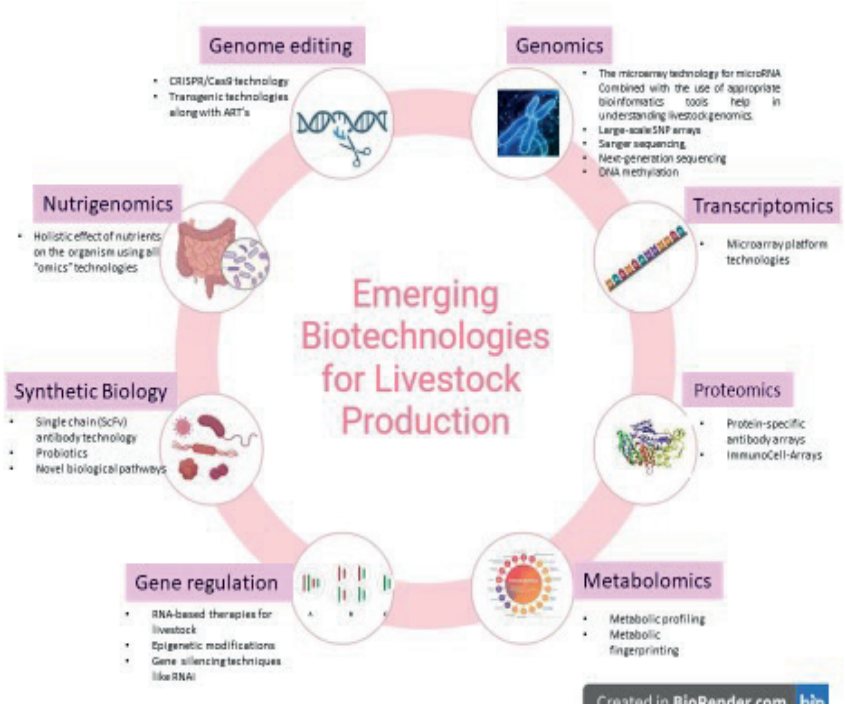


Figure 6. Emerging Biotechnologies for Livestock production; Livestock production rely more heavily on existing and emerging biotechnologies those including genomics, transcriptomics, proteomics, metabolomics, CRISPR, Nutrigenomics etc. (Gohar, Shah, Sarwar, Akram, & Mukhtar, 2021).

12. Summary

In conclusion, the symbiotic relationships between microorganisms and animals are complex and multifaceted, playing a crucial role in animal health, productivity, and sustainability. This chapter has explored the diversity of microorganisms in various livestock hosts, the different types of symbiotic relationships, and the mechanisms of symbiosis formation. We have also discussed the role of symbiosis in health and disease, antibiotic resistance, biotechnological applications, and future research directions. The study of animal-microbe symbiosis has significant implications for biotechnology and animal health, offering opportunities for improving livestock productivity, disease resistance, and environmental sustainability. However, there are also challenges and limitations to be addressed, such as the need for further research on symbiotic mechanisms and the development of effective biotechnological applications.

In addition, the study of genomics has greatly advanced our understanding of symbiosis as a common and vital aspect of life, particularly through the sequencing of genomes from organisms that cannot be cultured in a lab. Symbiosis is vibrant and transformative procedure where the

primitive partner granting the host innovative physiological talents, undergoes significant genetic and physiological changes assimilate into new culture, distinct from its free-living counterparts. The subject of NGP research is fast developing and has considerable potential for creating medicinal treatments. There is now more interest in discovering novel beneficial microorganisms for use in biomedical applications due to rapid advancement of sophisticated Genome analyzers, DNA decoding machines, and potent genome-editing utensils for bacteria. Novel molecular methodologies provide precise evaluation of the floral composition, leading to enhanced approaches to clarify the distinct mechanisms of action exhibited by probiotics in augmenting the performance of livestock animal species. Although a lot of research has been done, much more needs to be done to fully comprehend and utilize the advantageous properties of non-pathogenic bacteria. The properties of the pathogen and the host are what determine the host-pathogen interactions. Pathogens' aptitude to proliferate in their host species and spread to additional entities is a prerequisite for their reproductive success, which has led to the evolution of very diverse methods. In the future, to create our food animal farming will depend increasingly on recent and next biotechnology developments. Technological developments in molecular biology have given us new means of enhancing animal production, such as growth and yields, and have also made it possible to investigate the microbial lodgers of animals Product development and manufacturing optimization, especially concerning growth enhancement, disease tolerance and reproductive improvement. Through cloning techniques, we might eventually be able to create cattle that are free of prion, scrapie, and BSE by utilizing the DNA of naturally resistant animals.

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