Future of milk

I love animals and I love milk – what shall I do?

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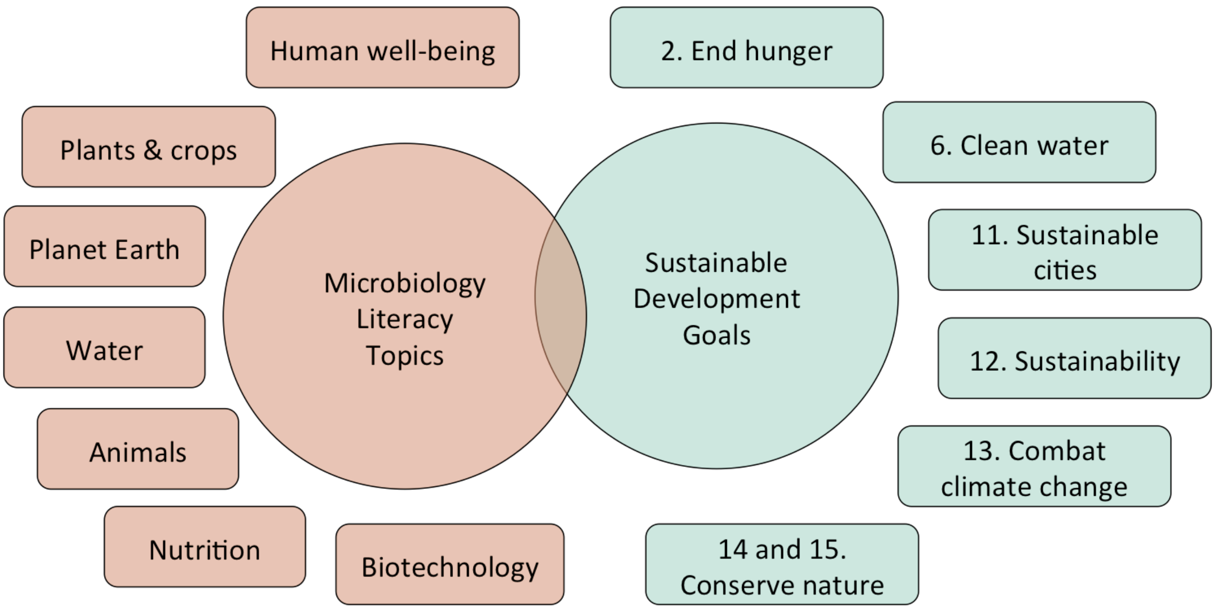
Storyline

Milk is widely consumed globally and especially by children. However, milk production is associated with a number of ethical, environmental and microbial challenges. To solve this, there are a number of plant-based milk alternatives. Yet, they often do not convince in taste and functionality, and are of poorer quality in terms of nutritional value and health. Consequently, innovation is needed. One option is to produce milk proteins **biotechnologically** in **genetically modified microorganisms**. Here, we discuss the opportunities and challenges associated with this approach.

The Microbiology and Societal Context

The microbiology: **zoonotic disease**, antibiotic resistance, animal **microbiomes**, human **microbiome** effects in nutritional changes; reduction in pollution and eutrophication. *Sustainability issues*: health; food and energy, economy and employment; environmental pollution; global warming.



Future of milk: the Microbiology

1. ***Challenges of current milk production practices***

a. **Milk production has a high environmental impact.** Dairy products come with a high climate footprint. This is due to a multitude of factors.

First of all, microorganisms in the gut of cows and ruminants in general are needed for the cows to digest plant materials such as grass that humans cannot digest. During the digestion process, these special microorganisms produce methane that the cow releases into the atmosphere. Methane is a potent driver of climate change. Consequently, farming high numbers of cows directly impacts climate change through the release of methane in the environment.

Methane production is particular pronounced in grain-fed industrially raised lifestock where both nutrition and lifestyle of the animals divagate from their natural habits.

In addition, the conversion rate of animal feed into milk is low. If humans were to eat the animal feed directly, we would need much less land for farming and human food production. Today, a substantial part of crops and beans are produced for animals instead of humans and are shipped around the world to serve as feed. The land used cannot be used for human nutrition or as natural habitats. In addition, pesticides and fertilizers are used in those areas. Thus, animal husbandry is a major contributor to land use, decreases biodiversity, and increases freshwater use, eutrophication, soil depletion and pollution. Today food production is the single most important driver of climate change and animal farming contributes to 80% of this footprint. Consequently, we need to consider alternatives to animal-derived products in future to ensure sufficient food for a growing world population, decreasing availability of farmland as a consequence of climate change, and to reduce the effects of climate change as much as possible.

b. **Farming cows for milk production raises ethical concerns**

It is likely that mammals like cows experience feelings in a similar way as humans do. Communication, different types of relationships and bonds between individuals have been observed. In developed parts of the world, we do not depend on consuming animal-derived products for our survival. Consequently, these products are a luxury but not a necessity. However, they come at a cost.

Male calves in milk-producing cow herds are killed, as they are expensive to raise without serving a purpose or monetary benefit. In order to obtain the milk from the mothers, female cows and calves are separated after birth and experience emotional pain resulting from not being together. Milk cows are bred to produce more milk than they would naturally do, often resulting in presumably painful udder strain and mastitis. In general, it is ethically questionable to exploit another species for our own luxury.

Finally, milk production is highly individual. The composition changes according to the age of the calf and its needs. It is a product tailored to bond a mother to her baby and to provide nutrition tailored to the baby's needs. It seems strange that humans blend milk that was created to serve individual needs, and drink it, despite the fact that it was designed to the needs of a different species in a different developmental state.

c. **Farming cows is associated with the spread of zoonotic diseases and antibiotic resistance**. Animals can carry diseases and as the SARS-CoV-2 virus recently demonstrated, some of these diseases are infectious and can be transferred between animals and humans. These so-called **zoonotic diseases** may be very harmful for humans and close contact between animals and humans, as is the case on animal farms, can increase the risk of transmission of these diseases. In addition, antibiotic resistance is an emerging problem for humans. Yet, the vast majority of antibiotics is administered to farmed animals which therefore serve as a reservoir of antibiotic resistance evolution and dissemination.

2. *Why do we like milk?*

a. **Milk is the raw material for many culturally-important food products.** Milk is the raw material to produce a number of culturally important and delicious foods including milk kefir, yogurt, crème fraiche and different kinds of cheese. Many of these products are actually produced through a fermentation process that involves microorganisms to transform milk into the desired products through their **metabolic** and **enzymatic activities**. In many cultures the majority of people use dairy products on a daily basis and moving to alternatives would be associated with changes in their habits, traditions and relationship with food.

b. **Fermented milk products are associated with health benefits.** Consumption of fermented foods is associated with a number of health benefits, including a more diverse human gut **microbiome** and reduced inflammation. While vegetable and bean-based fermented foods are common in Asia and Africa, Europe and the US mainly consume fermented milk products.

c. **Milk has a high nutritional value.** As milk evolved as sole feed source for mammalian babies, it is nutritionally nearly complete, dense and easily digestible, wherefore it is an attractive and nutritionally important food for humans. Milk is composed of more than 300 components including various proteins with bioactive functions, fats, and **antibodies** against diseases, and raw milk carries even microorganisms that are helpful to establish a healthy gut **microbiome** and digest milk efficiently. Milk also contains **lactose** that allows the growth of specific bacteria both in the fermentation process but also in the human gut. Some of these are lactic acid bacteria that are generally associated with health benefits and are often used as probiotics to increase human gut health.

d. **Milk contains bioactive particles.** Many ingredients of milk show biological activity. For example, some of the **antibodies** and **enzymes** in milk have antimicrobial properties and prevent growth of pathogenic bacteria or fungi; peptides derived from the major milk proteins, caseins, that occur during digestion and fermentation of milk, have shown to have pain relieving effects similar to **opioids**.

e. **Humans have evolved to milk consumption.** All mammals, including humans are born with the ability to **enzymatically** break down **lactose**. Humans have **evolved** to animal milk consumption since parts of the human population keep the genetic ability to digest milk also as adults. In addition, some cultures for example found in Mongolia rely heavily on milk consumption despite their genetic inability to digest **lactose**. It was found that their **microbiome** is enriched in species that digest lactose. Consequently, humans have **evolved** or have adapted **microbiomes** to allow them to utilize milk as food also as adults.

3. ***Finding milk alternatives.***

a. **Plant-based milk alternatives.** Today, many different plant-based alternatives are available like grain, seed or bean-based milks. They usually imitate milk in colour and some aspects of its functionality like foaming. However, the mouthfeel, texture, taste and nutritional composition is different to cow's milk. Usually, enzymes are used to create sugar from **complex carbohydrate**s present in the raw materials. Usually these sugars are **glucose**. Increased **glucose** consumption is associated with several health effects including a reduction in gut **microbiome** diversity and increase in inflammation in humans. In addition, the protein content of plant-based milk alternatives is usually lower than cow's milk and fats are added from plant-based sources. Many of the micronutrients, vitamins and health-promoting compounds that are present only in trace amounts in cow's milk are completely lacking. For example vitamin B12 is present in milk and can be better taken up from milk than from other sources, including supplements or meat. The improved bioavailability might stem from proteins found in trace amounts in milk that can bind and protect vitamin B12 up until digestion highlighting the complexity of nutrients and composition of milk for optimal nutrition.

b. **Prolonged breastfeeding.** Today, the World Health Organization recommends breastfeeding of infants for 2 years. Different cultures have different breastfeeding habits, but in times past it was normal to breastfeed up to 6-7 years of age. As toddlers and children usually consume much more milk than adults, it could be discussed to increase the recommendation of breastfeeding to ensure that humans optimally benefit from the tailor-made milk responding to their nutritional and health needs throughout their development, without harming or exploiting other species. In addition, human milk also carries gut microorganisms, and the skin contact between mother and child further increases the uptake of microbes in the children's gut, thereby increasing the gut biodiversity and resilience of the gut microbiome, and protecting children directly and indirectly from many diseases. In addition, breastfeeding also releases **oxytocin**, the love hormone that helps bonding between mother and children and has a relaxing effect. Consequently, longer breastfeeding can have benefits for the relationships between mother and children but must also be balanced with the freedom and independence of the mother.

c. **Production of milk components in microbial cell factories.** In order to create milk products that resemble natural milk, without harming the environment or animals, we can leverage microorganisms and new technologies. It is possible today to take genetic material, for example encoding proteins, from any source and to integrate this genetic material into microorganisms, which then express it. This so-called **genetic engineering** allows to make proteins from cows in microbial cell factories. Producing milk proteins in microbial cell factories is currently pursued by more than 20 companies and start-ups around the world (e.g. Perfect Day already sells products with recombinant milk protein). The microorganisms are grown in large **bioreactors** like in the beer brewing process and the proteins that are produced are purified and used to create milk-like products. While this development is very promising and fast, there are still many challenges to overcome:

Scientific:

i. there is a limit to how many compounds can be produced in an economically feasible way, so it will be difficult to recreate something resembling whole milk
ii. milk proteins are modified after their production in cows and humans but microorganisms do not do this naturally – these modifications however are important for their functionality (cheese melting) – so further research is needed to improve this, it is important to determine if there are any negative health effects associated with the consumption of large quantities of any recombinant protein that is not identical to the natural protein
iii. production of sufficient amounts of recombinant proteins is difficult
iv. the sustainability and economic feasibility of recombinant milk protein production needs to be established independently and probably standard processes have to be improved, for example by using waste streams or other sustainable substrates (like environmental CO_2) that can be used by the microorganisms for their growth and protein production

Infrastructure:

i. we need to build more fermentation infrastructure to allow scaled production of milk proteins.
ii. However, precision fermentation often requires specialized equipment, infrastructure and education, but food should be accessible around the world wherefore the equity question should be discussed and fair and just frameworks developed.
iii. Technological processes drive a detachment of humans from the food production chain. Historically food production was often a process where humans would be interconnected with the environment and take care for their environment.

Consumers:

i. need to be educated about the potential of **genetic engineering**

ii. need to have thorough safety training to ensure that trust in recombinant **proteins** can be established and maintained

d. **Future: blends, sustainable substrates, new proteins?** The creation of new milk will require thought around how milk should be designed. Should it be meant for adults or children, to drink or to produce cheese? For each scenario we should think what is important in terms of functionality and health and how can it be reached in an environmentally friendly way. Should the same proteins found in nature be produced or should they be optimized, for example to reduce their allergenicity or increase their nutritional value? Perhaps **recombinant** key **proteins** could be produced using waste streams as substrates and then mixed with a plant-based base. Maybe we do not even need to produce cow proteins but find microbial proteins that have the same nutritional value and functionality in food? The company Superbrewed has developed a cream cheese based on the proteins from a safe gut microorganism from humans that naturally contains more than 80% protein in its dry weight.

Relevance for Sustainable Development Goals and Grand Challenges

- **Goal 2. End Hunger.** Freeing land currently used for animal farming will allow us to use land on earth more efficiently to feed more people. In principle fermentations can be done anywhere in the world when the necessary infrastructure and knowledge to operate it is available. This renders the system very independent of local food and feed supplies and allows production even in resource-scarce environments.
- **Goal 3. Healthy lives.** It is important to understand the health benefits and risks of animal-derived products for humans to strategically design future replacement products that promote human health at least equally or even more than the conventional products and that have an equal or better nutritional composition.
- **Goal 6. Clean water.** Reducing animal farming will reduce water use and water pollution by animal wastes and agrochemicals associated with animal husbandry, including antibiotics and hormones used to promote weight gain.
- **Goal 11. Sustainable cities and settlements.** Recombinant milk and other milk alternatives may be produced locally to increase the sustainability of cities and communities.
- **Goal 12. Sustainable consumption.** We need to consider how we produce food in future and to include principles of circularity in our thinking. Due to the ability of microorganisms to degrade nearly all organic materials on earth, they are well suited to produce future food from waste resources in order to increase the efficiency of our food system. Genetic engineering of organisms also requires adequate safety controls and interventions to ensure that it conforms to societal requirements.
- **Goal 13. Combat climate change.** Reduction of animal farming will have a profound positive impact on climate change by reducing the carbon emissions.
- **Goal 14. Conserve marine resources.** Reduction in fertilizer use will decrease eutrophication and be beneficial for aquatic ecosystems.
- **Goal 15. Protect terrestrial ecosystems.** Reduced animal farming will, in addition to improving animal welfare and wellbeing, reduce land and water use, and pesticide and fertilizer pollution of the environment. This, and the resulting land surface freed up, will promote increasing biodiversity.

Potential Implications for Decisions

1. ***Individual***
    a. Should I consume animal derived products?
    b. How much and why do I consume replacement products?
    c. Would I buy products derived from genetically modified organisms?

2. ***Community policies***
    a. Health costs associated with unhealthy diets, zoonotic diseases and antibiotic resistance
    b. Promotion of plant or microbe-based alternatives to animal derived products.

3. ***National policies***
    a. Healthcare economics due to diets as well as zoonotic diseases and antibiotic resistance
    b. Environmental consequences of animal farming

Pupil Participation

1. ***Class discussion around the advantages and disadvantages of genetically modified organisms for food production***.

2. ***Pupil stakeholder awareness***
    a. Milk and recombinant milk production and consumption has positive and negative consequences for the SDGs. Which of these are most important to you personally/as a class?
    b. How would you solve the dilemma of wanting certain foods but knowing that their production and/or supply are environmentally damaging?
    c. Which choices do you have as an individual with regard to milk consumption?
    d. Would you be open to try milk produced from microbial protein or produced from genetically modified microorganisms?

3. ***Exercises***
    a. What should a healthy milk for adults and/or children be composed of?
    b. How can we ensure a transition from animal farming to a greener future and how can stakeholders such as consumers but also farmers be considered?
    c. If you were to advertise a milk product created with genetically modified microorganisms, how would you do this?

The Evidence Base, Further Reading and Teaching Aids

Examples of companies producing animal-free milk products
https://perfectday.com/
https://www.remilk.com/
https://www.superbrewedfood.com/
https://solarfoods.com/

Scientific literature:

Environmental impact:
https://ourworldindata.org/environmental-impacts-of-food?utm_source=baytoday.ca&utm_campaign=baytoday.ca%3A%20outbound&utm_medium=referral

Health:
https://www.tandfonline.com/doi/full/10.3402/fnr.v60.32527
https://www.sciencedirect.com/science/article/pii/S0899900713004607?casa_token=3aI853VJxO8AAAAA:h5LYHskPAvXvlOJWNOqfBTxV1yMJQvgD5Y7I2M5kDrvMD_R4Qv7dnri2LEY-6lxT09CufRUB
https://www.sciencedirect.com/science/article/pii/S0958694611000021?casa_token=DWG3hE_PbSkAAAAA:eSovwMiI_tDhJfVB5LJxu_egDmQtoAAVERX1VyMAsGGdfLpHHV6kt6s77jZKbJVb3EXTJ98C
https://www.sciencedirect.com/science/article/pii/B9780128144688000223

Recombinant production:
https://www.cell.com/cell/fulltext/S0092-8674(22)01515-X?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS009286742201515X%3Fshowall%3Dtrue
https://link.springer.com/article/10.1007/s002530000435
https://onlinelibrary.wiley.com/doi/full/10.1111/gcbb.12791
https://www.sciencedirect.com/science/article/pii/S1046592809003064?casa_token=f-JwKzXrR0YAAAAA:FS37gkiFufSj9z3Lx0Xl6xEdSZ22w271I8D1X31lt5_7CD7-p_BixjjFFmmLn57TmL26K_ic

Other:
https://gfi.org/industry/

Glossary

Antibody – An antibody is produced by the immune system of humans and other animals including cows to bind and inactivate potentially harmful substances such as bacteria, fungi, viruses but also toxins or foreign materials such as proteins

Bioreactor – A Bioreactor is a vessel that allows the controlled growth of microorganisms or cells, usually with the aim to produce many cells or specific products produced by these cells. Bioreactors usually allow the control of the environment such as temperature, oxygen availability, nutrient availability, etc., and may also allow to monitor these parameters as well as additional ones such as CO_2 production or pH.

Biotechnology – Biotechnology utilises living systems for the creation of specific products or processes we exploit. Examples can be beer brewing, but also advanced production of pharmaceutical drugs like insulin from microbial cultures.

Complex carbohydrates – Complex carbohydrates are long and structurally complex chains of sugar molecules. Examples are cellulose or starch abundant in most plant matter.

Enzyme/enzymatically/enzymatic activity – Enzymes are proteins and function as catalysts for specific chemical reactions. Enzymes increase the speed or enable chemical reactions.

Evolved/Evolution – Evolution is the adaptation of living organisms to changing environments over time.

Genetic engineering – Genetic engineering is a human activity that involves laboratory technologies applied to living organisms that can alter their genetic material. Genetic material is also naturally exchanged by microorganisms to a high extent. There are three ways microorganisms take up foreign genetic material – DNA – and integrate it in their own genome: free DNA can be taken up from the environment when the bacteria are in a so-called competent state (transformation); microorganisms can exchange genetic material present on small, auxiliary chromosomes called plasmids (conjugation); and microorganisms can become infected by viruses (phages) that insert their genetic material into the genome of infected microorganisms (transduction) – this also happens in humans upon some viral infections. Microorganisms naturally exchange genetic material frequently in order to adapt quickly to changing environmental conditions. They also have tools to incorporate viral DNA in their genome as a defense or immune system. The machinery in microbial cells to do this or to allow the insertion of foreign genetic material can be used and controlled by scientists to insert specific genetic information at targeted locations in the microbial genome. Consequently, genetic engineering is a rational human guided approach that uses naturally occurring tools and processes.

Genetically modified organism – A genetically modified organism or GMO is a living organism whose genetic material has been changed using specific genetic engineering tools by scientists.

Glucose – Glucose is the main sugar that human cells utilise as food. Free glucose can be found in some foods and many foods contain sugar chains that can be broken down to individual sugars including glucose.

Lactose – Lactose is only produced by lactating mammals. It is a simple sugar present in milk.

Metabolic activity/metabolism – Metabolism is the sum of all the chemical reactions taking place in a cell, including processes like the conversion of food into energy, the synthesis of cellular materials, etc., often via complex highly integrated and regulated pathways. Food will not be completely converted into energy but also additional by-products or cellular building blocks. Pathway intermediates and by-products are called metabolites.

Microbiome – The microbiome is the ensemble of all live bacteria, viruses and fungi and their genes associated with an individual organism. In the human context we often speak of the skin microbiome, the oral microbiome, the vaginal microbiome or the gut microbiome, which indicate the location of the collection of all microorganisms that can be identified there.

Oxytoxin – Oxytocin is a human hormone that plays a crucial role during pregnancy, childbirth, nursing, as well as romantic and other deep relationships. It is also called the love-hormone and facilitates bonding, well-being and relaxation.

Recombinant protein – A recombinant protein, is a protein that was produced by a genetically modified organism that naturally does not have the ability to produce this protein.

Zoonotic disease – Zoonotic diseases are infectious diseases caused by viruses, bacteria, fungi or parasites found in animals that have the ability to spread to humans and infect them as well.