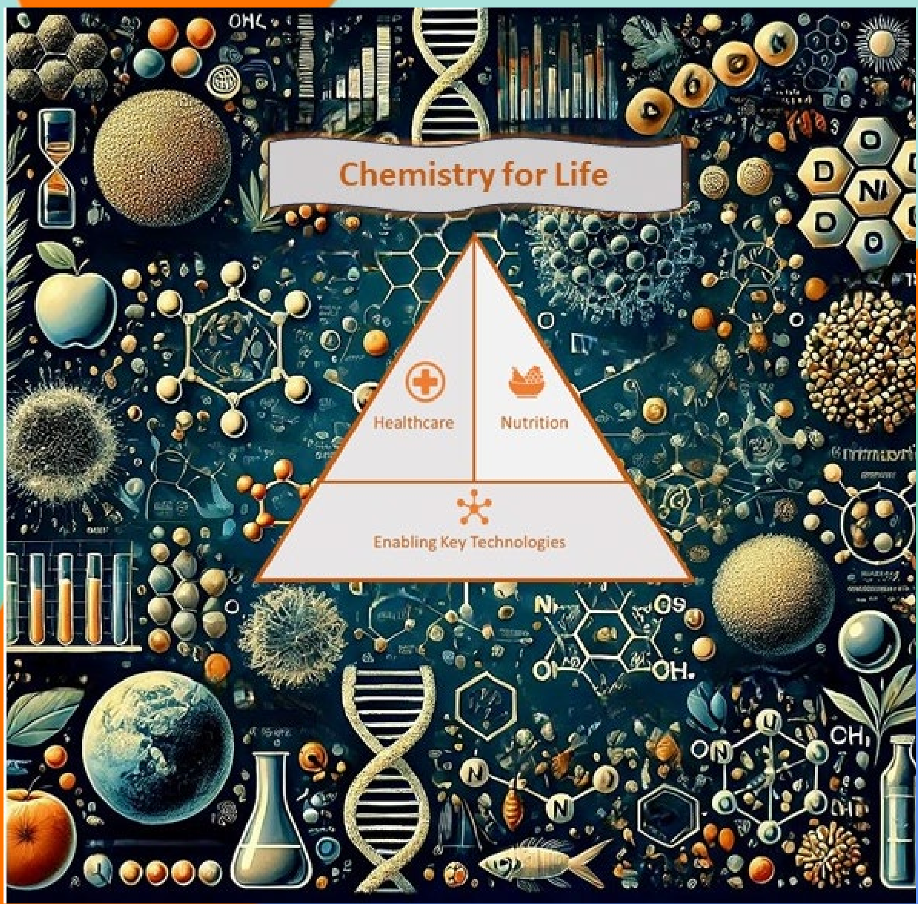
ChemistryNL

Roadmap

Chemistry for Life



Content

1. Introduction

Chemistry in all its facets is the most important enabler of technologies and processes that contribute to a more sustainable, healthier world. ChemistryNL aims to work on solutions for major societal challenges, based on green chemistry, circularity and a biobased economy.

"Chemistry for Life" is defined here as the application of chemical principles and knowledge to understand, improve, and sustain life in various aspects, including biological, medical, nutritional, and environmental fields. It encompasses the study of chemical reactions, structures, and properties of molecules and materials relevant to living organisms and their interactions with each other and the environment. This includes fields such as healthcare, food and nutrition, material sciences and sustainable chemistry with the ultimate goal of improving human health, well-being, and the environment. The Roadmap Chemistry for Life will serve as guidance to address the scientific challenges and opportunities in the fields of healthcare and food and nutrition, with a keen eye for sustainable impact, by utilizing enabling technologies.

1.1 Healthcare

Many human diseases are the result of altered or malfunctioning molecular/cellular mechanisms and genetic mutations. Detailed understanding of cellular wiring in the normal and, by contrast, the diseased states is essential to develop new drugs, biomaterials and diagnostic approaches to discover and prevent diseases, or re-program and revert cells to a normal healthy state or trigger cell death (apoptosis) to eliminate defective cells. Fundamental disciplines including molecular biology, biochemistry, medicinal chemistry, material science and computational modelling together allow us to study the relevant interactions and events disturbed in disease and targeted in therapy. With the help of chemometrics and artificial intelligence (AI), the identified health(care) related chemical processes will enable the development of novel or improved drugs with a personalized and more precise effect, the repurposing and sustainable use of existing drugs, the development of new diagnostic tools and the design and engineering of new biomedical materials.

Environmental issues, climate change and shortage of raw materials urge for a sustainable and/or targeted production of medicines, biomaterials and diagnostics to minimize the environmental impact and optimize resource utilization throughout the entire development and manufacturing process. Implementing Green Chemistry principles will be important, in which the use of hazardous materials is minimized, energy and resource consumption is lowered and waste generation is reduced by using safer solvents. Also more targeted medicines and increased bioavailability will reduce the environmental impact `by reducing unnecessary waste and reduced use in patients not susceptible to therapy. If possible, biological production systems are leveraged, such as microbial fermentation and cell culture in different fields of biotechnology. By integrating these strategies into drug manufacturing, diagnostics and biomaterials development and manufacturing processes, companies can reduce their environmental footprint, conserve resources, and contribute to a more sustainable healthcare industry.

Biotechnology in healthcare relies heavily on chemistry, particularly biochemistry and molecular biology, to understand and manipulate biological processes. Chemistry provides the tools for designing and synthesizing biomolecules, such as enzymes, antibodies, and nucleic acids, which are central to biotechnological applications. It is also crucial in drug development, helping identify and optimize compounds for therapeutic use. Additionally, chemistry plays a vital role in creating diagnostic and monitoring tools, such as biomarkers, chemical assays, and reagents, which enable early disease detection, accurate monitoring of disease progression, and the assessment of treatment efficacy. These advancements are key in personalized medicine and in the development of point-of-care testing technologies, making healthcare more precise and accessible. Through these contributions, chemistry enables biotechnology to drive innovations that significantly enhance health outcomes and patient care.

Overall, the aim is that chemistry contributes to the KIA Health & Care with the mission that by 2040, all Dutch citizens will live at least five years longer in good health and with better quality of life, and health differences between the lowest and highest socioeconomic groups decreased by 30%, leaving as little carbon footprint as possible.

1.2 Food and nutrition

Chemistry is an essential element in nutrition and food innovation. Chemistry enables the food (and feed) sector to get to the next level in answering fundamental scientific questions to provide breakthrough innovations that address societal needs related to health, food quality and security throughout the whole lifespan.

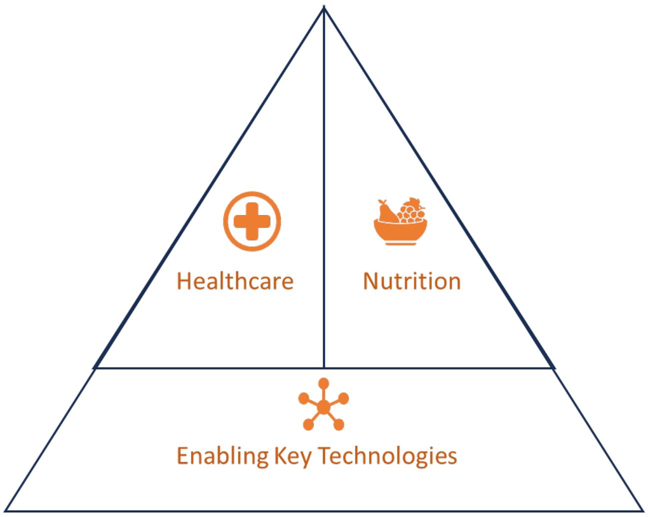
Food and nutrition play a significant role in maintaining overall health and well-being. Food provides essential nutrients that support body functions, growth and development. Different foods contain various nutrients, including carbohydrates, proteins, fats, vitamins, and minerals, each serving specific functions in the body. The risk of obesity and related health conditions such as type 2 diabetes, cardiovascular disease, and certain cancers are related to food and nutrition. Food allergies and intolerances can also have significant implications for health and quality of life. On the other hand, a balanced diet rich in fibre, prebiotics, and probiotics supports a diverse and healthy gut microbiome, which is associated with better digestion, immune function, and overall health. Molecular biology, biochemistry, food chemistry, materials science, and computational modelling can elucidate the critical interactions and processes involved in the relation between food and nutrition and health and disease.

Sustainable food production and an increased contribution of renewable (plant-based) food to the diet require new insights and understanding of food at the molecular level. This way, (bio)chemistry supports the missions formulated in the KIA Circular Economy which also aims for optimal use of resources, including biological resources and manufacturing processes.

Chemistry and biotechnology fields are closely intertwined in driving innovation and improving food systems. Biotechnology leverages chemical principles to develop bio-based solutions for food production, such as genetically modified crops with enhanced nutritional content or resistance to pests. It also aids in the fermentation processes used to produce probiotics, vitamins, and bioactive compounds that improve human and animal health. Additionally, biotechnology is instrumental in creating sustainable and efficient feed formulations for livestock by developing microorganisms that enhance nutrient absorption or break down complex feed ingredients. Together, chemistry and biotechnology enable the development of functional foods, enhance food safety through bio-diagnostics, and support the creation of innovative, sustainable practices in both human nutrition and animal feed, addressing global food security and health challenges.

The goal is that chemistry contributes to the KIA Agri & Food with their mission that by 2050 the Dutch food system will be ecologically, socially and economically sustainable but also tasty, healthy and safe.

A three-pillar roadmap has been developed to address the key scientific challenges and economic opportunities in Healthcare (vertical Pillar 1) and Food and Nutrition (vertical Pillar 2), which are interconnected by Enabling Technologies (horizontal Pillar 3) (See figure below).



Key Challenges & Tasks Overview	
Healthcare Task 1	Development of analytical and diagnostic devices and cellular model systems
Healthcare Task 2	Creation of new molecules and cells for disease treatment and prevention in a sustainable way
Healthcare Task 3	Biomedical materials for improved functionalities
Food and Nutrition Task 1	Biochemical tailoring of food
Food and Nutrition Task 2	Understanding food digestion and metabolism to increase nutritional availability and health
Food and Nutrition Task 3	Sustainable production and consumption
Enabling Technologies Task 1	Bio)chemical processes from molecule to organism
Enabling Technologies Task 2	Engineering of molecules and cells
Enabling Technologies Task 3	Applying Green Chemistry Principles
Enabling Technologies Task 4	Development of analytical tools

2. Key challenges

2.1 Pillar 1: Healthcare

Pillar 1 focuses on Healthcare, and more specifically on 'Molecules, analytical devices and approaches for understanding, developing, monitoring and improving precision healthcare in a sustainable way'. Chemistry contributes to health and disease through drug discovery and development, personalized medicine, diagnostic technologies, biomedical materials, understanding disease mechanisms, and assessing environmental and lifestyle factors. By leveraging chemical principles and techniques, we aim to advance our understanding of disease processes and well-being, develop more effective treatments and materials, better diagnostics and improve patient outcomes, while implementing and using sustainable ways of development and manufacturing.

Several challenges persist in healthcare, amongst which healthy ageing is one of the most prominent issues. The ageing population, coupled with lifestyle factors, has led to an increase in the prevalence of diseases such as Alzheimer, diabetes, cardiovascular disease, and cancer. These diseases involve intricate biological pathways and interactions. The development of new molecular entities, devices and approaches, including chemometrics and AI, are relevant for improving diagnosis, monitoring and personalized treatment. Insight into specific molecular defects and targeting of these appear effective, but because of the complexity not all molecular defects of them can overcome treatment failure and recurrence. More detailed and personalized understanding of the complex responses based on understanding of the integrated chemical network of cells is key. This is equally relevant for diseases of tissue degeneration (neurodegeneration, circulatory system, joints) where chemical clues can be used as early warning and biomaterials need to be designed to reach or replace the specific sites involved and have the desired regenerative effect.

Another challenge is that drug and biomaterials development is often hampered by insufficient preclinical models, such as personalized or multicellular cell cultures and animal models. Better and different models (including animal-free models based on artificial intelligence) are needed, as existing models often have limitations in accurately predicting efficacy and toxicity in humans.

Sustainability of drug production remains challenging, due to the complex nature of pharmaceutical manufacturing and supply chain processes (from raw materials to drug product and packaging and delivery) , the need for large quantities of water, fossil derived raw materials, energy and the generation of hazardous waste. (Bio) Process technology, including process intensification techniques and green chemistry principles are needed to be designed in a sustainable and safe manner to tackle these challenges.

Advancements in fields such as genomics, proteomics, metabolomics, in vitro models and AI hold promise for overcoming these challenges, while the environmental impact and optimization of resource utilization also need to be taken into account. The tasks that contribute to tackling the challenges in Healthcare will be described here in further detail and directly support the KIAs Health & Care and Key Technologies.

2.1.1 Healthcare Task 1 : Development of analytical and diagnostic devices and cellular model systems

Most human diseases are the result of altered and/or malfunctioning of molecular and/or cellular mechanisms and genetic mutations. The molecular basis of disease is often poorly understood. Moreover, current therapies appear effective for a subset of patients and ineffective for other patients where for example drug resistance may occur. Quantitative patient-derived omics analysis and model-based predictions (using big data and AI) constitute a treasure trove to understand which molecular pathways are affected and may be targeted by (existing) drugs, thus offering an avenue towards better (companion) diagnostics and precision medicine. The development of test systems, that enable citizens (not only patients) to self-monitor their health status would enable better (preventive) care system.

To achieve this:

We need to explore and develop analytical and diagnostic devices, cellular model systems, computational models and approaches for monitoring, understanding and target identification to improve more precise (personalized) and effective healthcare. Application of novel sensor systems also include low cost, non-invasive systems to monitor the nutritional status of cells and their response to food and nutritional ingredients. This is related to the KIA Key technologies and also in line with the KIA Health & Care which aims for better (health)care in the home environment.

Specific steps required present-2040:

- Development of diagnostic workflows/devices.
- Establish large-scale multi-centre infrastructures for the quantitative chemical analysis of all bio-molecular entities such as the Future Medicine Initiative, Oncode Accelerator, Biotech Booster etc.
- Determine which biomolecular entities and combinations are relevant/robust to predict disease state, prognosis, treatment options and or treatment success.
- Development of high-throughput novel diagnostic analytical workflows and devices for (multifactorial) diseases.
- Translation into ultra-sensitive, easy-to-use, low-cost micro-devices useable in precision healthcare and as companion diagnostics.
- Development of easy-to-use, low-cost microdevices that are indicative of disease onset, therapy efficacy, for at home use.
- Obtain novel insights into molecular mechanisms of disease.
- Develop novel synthetic and cellular platforms/model systems (e.g. patient-derived pluripotent stem cells (iPSCs); CRISPR-Cas KO/KI cells; primary cells; derived cells/organoids; 3D cellular co-culture systems; organoids; multiplex high content imaging), analytical tools and computational models for networked biochemical processes, diagnosis and intervention.
- Identify sets of molecular components, interactions and complex signalling networks representative for disease state or response to treatment.
- Implement AI-based approaches and network-based analysis of diseases using chemo-/bioinformatics, pharmacogenomics and systems biology to understand the relationship between human physiology, the microbiome and the environment.
- Identify critical and accessible steps in molecular pathways and networks for novel diagnostics, (multifactorial) intervention and targeting.

Milestones:

- Personalized omics analysis, relevant robust markers of disease process identified and validated.
- Establishment of personalized (iPSCs-based) (2/3D) multi-cellular model systems (cells/organoids).
- Target identification for (multifactorial) diseases.
- Enabled AI-based and network-based analysis of disease based on quantitative profiling of patient material using chemo-/bioinformatics, pharmacogenomics and systems biology.
- Device (multi-) targeted therapies for (multifactorial) diseases.
- Developed novel clinically affordable disease-oriented workflows and devices.

- New and affordable personalized diagnosis and preventive care.

Expected results present-2040:

Scientific/technological goal:

- Diagnostics and target-based treatment established on disease network analysis.

Industrial end goal:

- Translation of diagnostic tools and analysis to commercialization.

Societal goal:

- Cohort of patients performing self-diagnosis or self-monitoring of health status thus contributing to the KIA Health & Care central mission. The central mission aims that Dutch citizens live longer healthy lives for at least 5 more years and the difference between the highest and lowest socio-economical layers decrease by 30%. This task also contributes to mission 2 of KIA Health & care which aims better health care at living (home) environment.

2.1.2 Healthcare Task 2 : Creation of new molecules and cells for disease treatment and prevention in a sustainable way

Over the last decade, advances in genetic and proteomic analysis have led to the identification of a large set of genes/proteins that play a key role in disease. It is an enormous challenge to determine which of these genes/proteins are suitable drug targets. These target genes and proteins need to be studied on a molecular level and their activities perturbed with small-molecule compounds, biologicals or genetics to validate them as 'druggable'. This offers enormous opportunities for the Netherlands and especially for chemistry in the life sciences field. Chemistry is key in the development of novel assay technologies, diagnostic agents and it provides the starting point for the development of novel classes of drugs in areas of unmet needs. An investment in target validation on a molecular level, small molecule screening, medicinal chemistry, antibody-based approaches, AI and big data analysis will allow the development of small molecule drugs/biologicals that allow more effective and affordable treatment of disease.

To achieve this:

In order to translate current genetic, metabolomic and proteomic knowhow into novel therapies, several steps need to be taken including strengthening of specific expertise and infrastructure establishment. Examples of opportunities for drug development include novel drugs/biologicals that can be used to treat cancer, infectious-, metabolic-, auto-immune-, neurodegenerative- and genetic diseases as well as medication that acts on the central nervous system and drugs that aid tissue regeneration. Likewise, opportunities exist for the development of biologicals and cell-based therapies and creation of new chemical, molecular and cellular entities. Novel chemical probes and assays need to be developed for detailed studies of targets on a molecular level. Simultaneously such probes may aid the development of diagnostic agents.

Specific steps required present-2040:

- Assay development for selection of bioactive (bio)molecular entities.
- Development of novel miniaturized assay formats for High Throughput Screening (HTS) and fragment-based approaches (e.g. FRET, fluorescence polarization, activity-based profiling) for identification of well-defined target selective new chemical entities (NCEs) and biologicals.

- Validation of assays for high content screens and cell-based assays for identification of well-defined target selective NCEs and biologicals.
- Development of target or class specific probes for studies of drug action in cells and animal models. These probes also offer opportunities for the development of diagnostic and imaging agents.
- Sustainable design and synthesis of new (bio)molecular entities, following principles of green chemistry, which enforces the cluster Chemical technologies in the KIA Key Technologies.
- The development of novel bioactive molecules that can serve as therapeutic agents by means of synthetic or biochemical programs. Further characterization of novel (bio)chemical entities, and the cellular processes and networks they act on.
- Precision medicine. Development and application of tailor-made NCEs and biologicals aimed at (families of) disease-related targets (for unmet disease areas).
- Development of first tool compounds/biologicals, which are entities that validate molecular targets for the treatment of specific diseases.
- Development of candidate drugs that act on targets validated with tool compounds.
- Development of matching probes that can be developed into imaging and diagnostic agents.
- Development of smart delivery and smart formulations for local delivery, in combination with artificial intelligence and on line monitoring.
- Structure-based drug design (SBDD).
- Obtain structural information of target protein (e.g. X-ray, Cryo-EM, NMR) to develop 3D molecular models of targets.
- Binding mode prediction and (virtual) screening for selection of candidate molecules.
- Dynamics of drug-target interactions (e.g. single molecule conformational dynamics).
- Parallel high throughput crystallography and structure determination.
- Design and optimization of molecular entities.
- Computational-based modeling approaches implementing AI-based de novo design of molecular entities and biologics, fragment-based drug discovery, machine-learning based virtual screening, and structure-based drug discovery (using experimental structures, Alphafold and homology models).
- Sustainable medicines production.
- Development of novel methods for more sustained manufacturing of medicines.
- Reduce, replace and eliminate use of hazardous solvents during medicines manufacturing.
- Use of (bio)catalytic approaches.
- Modern and more energy efficient manufacturing methods like (photo) flow manufacturing and electro chemistry.
- Reduction in use of water and disposables, especially in Cell Culture based processes.
- Reduction and elimination of residual quantities of medicines in (waste) and surface water.
- Smart formulations increasing bioavailability and reducing API use and waste.

Milestones:

- Sustainable development of NCEs, biologicals, cell and gene therapies and bio-conjugates for use in therapy, diagnostics, in vivo imaging, and clinical applications.
- Omics data exploited by the development of novel tool compounds and matching diagnostic probes.
- Proof of Concept realized for several NCEs, biologicals in Phase 1 and phase 2 clinical trials.
- Structural information on the interaction of NCEs, biologicals and bio-conjugates with target proteins available.

- Outreach to partners with relevant targets.
- Further development of drug candidates, biologicals and smart formulations into new affordable medicines and affordable entities for diagnosis and therapy, suitable for diverse SocioEconomical Segments (in relation to KIA Healthcare central mission).
- Coordinated small molecule synthesis, medicinal chemistry, chemical biology and smart formulation based approaches with reduced environmental footprint and central screening and characterisation both in vitro and cell-based and high content.
- Public-private partnerships for further development of NCEs and smart formulations.

Expected result present- 2040:

Scientific/technological goal:

- Development of (bio)molecular entities for therapeutic applications in an environmentally friendly way.

Industrial end goal:

- New high quality NCEs, biologicals and smart formulations for further development towards marketed drugs that serve unmet medical areas. Establishment of novel ventures.

Societal goal:

- New drugs leading to healthier living, healthy ageing, better health(care), and better understanding and control of disease by affordable small molecules or biologicals suitable for diverse Socio Economical Segments (in relation to KIA Healthcare central mission).

2.1.3 Healthcare Task 3 : Biomedical materials for improved functionalities

Development of improved biomedical materials to reduce the burden for a variety of diseases offers an important solution to unceasingly rising healthcare costs and requirements for a better quality of life. Biomedical materials can improve the performance of for instance implants, medical devices, scaffolds and drug delivery systems. Furthermore, superior biomedical materials may help minimize side-effects and the need for invasive surgery.

To achieve this:

In order to generate novel and improved biomedical materials for safe, cheap and widespread use in surgery and monitoring of disease, several phases of the innovation pipeline need to be strongly connected. Aspects of fundamental chemical research for improved functionalities, green production processes and medical evaluation for in vivo use are to be jointly tackled. Examples of application areas for improved biomedical materials include in vivo sensors, cardiovascular surgery, oncology, musculoskeletal, nephrology, drug delivery systems and implants. This is related to the KIA Key technologies.

Specific steps required present-2040:

- Understanding material properties contributing to improved compatibility in human cells.
- Explore new functionalities of biomaterials in human bodies (e.g. stability, release, mechanical, strength, lubrication, biosafety and toxicology and antimicrobial).
- Sustainable development and production of new materials and devices.
- Piloting and commercialization of new materials and devices.

Milestones:

- Capable to design materials which are compatible in humans.
- Multiple in vivo sensors applied.
- Principles of Green Chemistry applied to the development and production of biomaterials and devices.

Expected result present-2040:

Scientific/technological goal:

- New leads for Biomedical Materials developments established, Dutch centres of excellence and international network established (PPPs).

Industrial end goal:

- High quality biomedical materials with wide array of application areas and large market potential in medical interventions.

Societal goal:

- Improved health care due to improved quality of life, reduced side effects or need for invasive surgery thus contributing to the KIA Health & Care.

2.2 Pillar 2: Food and Nutrition

Pillar 2 focuses on Food and Nutrition, and more specifically on 'Molecules, analytical devices and approaches for understanding, monitoring and improving food to ensure a sustainable supply of safe, nutritious, delicious food and feed to optimize health and wellbeing'.

Chemistry plays an important role in food and nutrition, spanning from understanding food composition, digestion and processing to ensuring safety, quality and nutritional value. Its applications contribute to addressing challenges in food security, health and sustainability.

The correlation between food composition, microbiome and disease allows for the tailoring of food to promote a beneficial health status and microbiome (in some cases disease-specific). Food and diet can also be tailored to promote a healthy immune system with the food being a source of therapeutic agents. For this all there is a strong need to know what nutritional components are crucial for maintaining and regaining health and preventing specific diseases. More and more receptor-based assays are employed to understand the impact of dietary constituents on human metabolism, including flavour perception and health status. Understanding food digestion and metabolism to increase nutritional availability and health is also pivotal.

Ensuring the safety of the food supply chain is a significant challenge. Chemical contaminants such as pesticides, heavy metals, food additives, microplastics and mycotoxins can pose risks to human health if present at unsafe levels. Food fraud, including adulteration and mislabelling, poses risks to consumers and undermines trust in the food supply chain. Chemistry plays a vital role in developing analytical methods to detect and quantify contaminants, as well as in designing strategies for their mitigation and control. In addition, analytical methods are needed to authenticate food products and detect fraudulent practices. Techniques such as DNA testing, isotopic analysis, and spectrometry / spectroscopy help verify the origin, authenticity, and quality of food (ingredients).

Food waste and industrial byproducts are significant issues that have environmental, economic, and social implications. With respect to the former, chemistry can contribute to developing innovative techniques for food preservation, packaging , and processing to extend shelf life and reduce waste . Additionally, chemical processes such as enzymatic digestion and fermentation can be employed to convert food waste into value-added products such as biofuels, enzymes and bioplastics. With respect to the latter, much effort is dedicated to fully utilizing agricultural raw materials, by setting up new biorefinery strategies. An illustrative example of this is the extensive utilization of potato tubers, which now not only provide high quality starch, but also fibre and high quality proteins. The same holds for yeast from the beer brewing process, which is now developed into a protein resource. The tasks that contribute to tackling the challenges in Food and Nutrition will be described here in further detail.

2.2.1 Food and Nutrition Task 1: Biochemical tailoring of food

Consumers have increasing demands for the quality of their food. To improve food quality in terms of texture/flavour (sensoric experiences) and health related issues, foods can be tailored by physical as well as (bio)chemical ways. With advances in biochemistry and compositional combined with computational analysis (including chemometrics and AI approaches), additional means became available to understand and modify foods and/or ingredients in a precise and also more sustainable way. Such developments are of crucial importance in the transition away from animal-based protein supplies towards more environmentally friendly plant-based protein sources with their associated reduction of greenhouse gas emissions. They support the missions formulated in the KIA LWV, the KIA CE as well as enforcing the cluster Life Science Technologies in the KIA Key Technologies. (Biochemical) tailoring to exploit the versatility of food and food ingredients with optimal processing, flavour and texture will allow us to turn plants into tasty, safe and nutritious foods.

To achieve this:

Although the biochemical pathways leading to the accumulation of precious food ingredients are known, complete utilization of plant produce still confronts us with challenges: (i) Ingredients themselves display suboptimal performance in applications; (ii) Co-extracted substances spoil the appreciation of certain plant ingredients; (iii) Yields of the target ingredient are often too low. With respect to (i) most attention has been focused on macronutrients (carbohydrates, proteins and lipids) and hydrolytic enzymes to improve their functionality (removal of glycosyl side chains for gelling, degradation for making protein hydrolysates, interesterification for melting point engineering, respectively). With improved analytical techniques, it now becomes feasible to direct such reactions more precisely, and additionally oxidative enzymes have entered the scene with numerous potential applications with respect to generating flavours, health-promoting substances and food preservatives. With respect to (ii), co-extracted substances, or so-called co-passengers, are often bitter or astringent, which hampers the liking of plant-based meat alternatives by consumers. Besides, enzymes endogenous to the plant are often co-extracted with the plant proteins, which create undesirable off-flavour or off-colour during processing of the raw material, or later on in the food products. With respect to (iii), secondary plant metabolites like flavonoids, etc., can serve as flavour, health-promoting substance or natural food preservative, but usually their amounts are too small to be economically competitive. These high added value compounds might eventually be produced by fermentation with engineered microbial strains, facilitating higher yields, as well as easier isolation.

Specific steps required present-2040:

- Identify relevant flavour forming reactions in foods and fermented foods that have to be enhanced or inhibited, both in situ in foods and ex-situ productions of flavours.
- Quantify intermolecular interactions in foods and understand how molecules build multiscale structural organisations affecting e.g. protein binding, which flavours release and uptake of nutrients.
- Identify suitable health promoting substances that are formed by a limited number of enzymatic reactions, using microbes or that are plant derived.

- Produce and apply enzymes or microbes to efficiently generate, improve or stabilize flavour and health-promoting or in foods and/or ingredients.
- Design efficient strategies for cofactor regeneration to drive the (bio)synthesis or modification of ingredients more efficiently.
- Enhanced production of taste, nutrition and health promoting substances within the food matrix.
- Design cascading enzyme reactions including activation of desired ingredient nutrient formation routes and inactivation of formation routes of off-flavours or natural toxins or anti-nutrients.
- Connecting sensory science (incl. texture/flavour combination) with molecular (receptor-ligand) understanding to guide food tailoring.

Milestones:

- Insight in, and control of, formation routes of off-flavours, toxins and anti-nutrients in plant-based materials
- Improved nutrient delivery through controlling protein/small molecule interaction
- Molecular understanding of factors impacting texture/flavour/health.
- Novel enzymes/microbes that tailor texture/flavour both in situ and ex-situ.
- New, biochemically derived health promoting substances, including enzymes and micro-organisms.

Expected result present- 2040:

Scientific/technological goal:

- Improved insight in biochemistry of processes occurring during food and food ingredient production.

Industrial end goal:

- More controlled tasty and healthy food, personalized food. Increased flexibility in terms of raw materials.

Societal goal:

- Longer shelf life of food products and less waste due to too low flavour or off-flavour formation. All food produced in a circular manner with limited environmental impact.

2.2.2 Food and Nutrition Task 2: Understanding food digestion and metabolism to increase nutritional availability and health

An important mission to improve the value of food is increased nutritional availability and contribution to health. Modern urban populations suffer from the so-called “triple burden” of malnutrition, by which the coexistence of hunger, nutrient deficiencies, and excess intake of calories leading to overweight and obesity create a serious threat to human health. Increased nutritional availability and improved health status by (bio)chemical advances and improved understanding of nutrition and health will greatly reduce this health threat.

To achieve this:

Increased efficiency of use of foods by increased nutritional availability of food constituents is needed. Key to this is the understanding of the molecular processes and interactions taking place during the digestion of foods, including the role of the gut microbiota. Evidence accumulates that the microbiota composition determines the health status of an individual. Besides typifying the composition of the gut microbiome, it is also important to monitor the transformations occurring in the gut. For instance, prebiotic oligosaccharides are converted to short chain fatty acids by beneficial microbes, providing a health benefit to the host. Moreover, phenolic compounds can be modified by gut microbiota, leading to altered bioavailability of the compounds and sometimes also bioactivity. By mapping microbiota composition and conversion of dietary molecules, an enormous amount of data will be generated, ranging from digestion kinetics of the dietary compound to many specific metabolites formed upon passage through the gut. These data need to be connected to targets (e.g. receptors) and / or processes (e.g. energy metabolism) inside the human body. Eventually, this will require data science or AI approaches to scrutinize all information collected, uncover biomarkers for human well-being, and ultimately provide dietary advice at the level of an individual.

Specific steps required present-2040:

- Establishment of mechanistic molecular descriptors of hydrolysis/fermentation kinetics of food constituents, requiring detailed compositional analysis by e.g. LC-MS approaches.
- Establishment of physico-chemical descriptors of hydrolysis/fermentation processes of food.
- Establishment of quantitative correlations between the microbiota composition and the occurrence and/or formation of prebiotics during intestinal fermentation.
- Design of good in vitro systems to predict food digestion and contribution to health in vivo.
- Integration of molecular and physico-chemical parameters to describe the spatial and temporal resolution of food digestion/fermentation products in the digestive tract during consumption of foods for healthy and diseased individuals of different ages (from new-borns to elderly).
- Correlate in vitro and in vivo digestion models to explain what happens during digestion in humans and decipher the full functionality of the whole GI tract including flavour and texture sensing.

Milestones:

- Quantitative and mechanistic models of in vitro and in vivo digestion of foods based on biochemical properties of food constituents.
- Correlation of in vitro and in vivo models.

Expected result present- 2040:

Scientific/technological goal:

- Improve insight in connection between nutrition and health by understanding digestion.

Industrial end goal:

- Foods with optimal nutritional value and related added value.

Societal goal:

- Foods with directed impact on the (bio)chemistry of health and disease. Thus supporting the central mission of the KIA Health & Care.

2.2.3 Food and Nutrition Task 3: Sustainable production and consumption

Accelerated globalization and raised living standards leading to increased production and consumption of food are progressively threatening our climate, deplete natural resources and have a negative environmental impact. Responsible food production and consumption is a crucial aspect of improved food security and availability. Hence, there is a need for the creation of an “efficiency revolution” in the use of agricultural raw materials by making consumer preferred products based on plant materials, developing new technologies for making conversions more efficient and by preventing wastes and nutrient losses without the use of undesired chemicals, thereby improving the sustainability of food supply. More specifically, tremendous effort is put in finding suitable alternatives for animal-based protein. Many alternatives are under investigation, the most promising of which are probably plant proteins, fungal proteins, and proteins obtained by so-called precision fermentation. Each of these alternatives have their pro's and con's. Plant proteins are more sustainable, relatively cheap, but suffer from usually poor water-solubility, presence of undesirable co-passengers (small molecules, but also endogenous enzymes leading to off-taste and off-colour formation). Existing products like Quorn are fungal protein-based, but there is room for fungal alternatives with different / improved flavour and / or texture. Precision fermentation is relatively expensive, but the opportunity of producing highly functional proteins in pure form. Therefore, many challenges need to be tackled to efficiently use alternatives to animal-based proteins in food applications. At the same time, sustainable consumption needs to be addressed. In this respect (open) shelf-life of food products will be important. There is a quest for less energy-consuming preservation methods. Natural, safe antimicrobial compounds will become more and more important to safeguard the open shelf-life of food. Mixtures of such compounds is thought to reduce the risk of antimicrobial resistance and should be addressed in this context. This enforces to develop cheap and efficient (electro)chemical processes for the food and chemical industry, explicitly including the required scaling of these processes.

To achieve this:

- Food manufacturing should be carried out in a more sustainable manner than today. Important areas of attention to be elaborated on in this aspect relate to:
- More sustainable food and food ingredient processing by less use of chemicals, water and energy (low temperature processing).
- Food processes in concentrated and/or crowded systems.
- Replacing "chemical" extraction of ingredients by aqueous (enzymatic) processes with full recycling of extractants and processing aids.
- Higher crop yield and improved preservation of food.
- Understanding biochemical properties of terrestrial, aquatic or other raw materials for replacement of animal based foods/food ingredients (e.g. proteins).
- Less spoilage of foods by exploring biochemical production and use of new nature inspired preservatives, e.g. lipid stabilizers, anti-oxidants, phenolics and microbial preservatives.

Specific steps required present-2040:

- Development/adaptation of analytical methods to be used in concentrated and/or crowded systems.
- Understanding at a molecular level the contributions of individual components within complex ingredients as well as isolated ingredients from existing and novel sources.
- Understanding the fate of molecules in novel milder food processing methods.
- Identification of critical descriptors of enzyme function (selectivity, activity, stability, etc.) in concentrated/crowded systems.
- Identification of highly selective and effective enzymes to release ingredients and/or to produce ingredients from raw materials.
- Control of biochemical conversion reactions which deteriorate the properties of ingredients obtained from novel sources.

- Understanding functionality of food ingredients, (e.g. proteins) from a molecular perspective, taking into account also intermolecular interactions and environmental factors, thereby enabling implementation of existing and new food sources.
- Targeted modification of food ingredients from existing and novel sources to enhance functionality and use.
- Establishment of mild-chemical, enzymatic or microbial routes to produce ingredients.

Milestones:

- Identification of new, sustainable sources for protein supply including methodologies to convert these into safe and nutritious, consumer-preferred products.
- Novel biochemical processes for obtaining ingredients with reduced environmental footprints.
- Mild processing routes retaining all positive nutrients while preserving quality and safety of the food.
- Replace unhealthy food additives that are used to reduce spoilage by novel healthy alternatives.

Expected result present-2040:

Scientific/technological goal:

- Understanding biochemical conversions in complex matrices and concentrated systems. Understanding biochemical production routes for new antimicrobials.

Industrial end goal:

- Improved sustainability of food production and consumption.

Societal goal:

- More efficient use of food and food ingredients to address food security and environmental burden.

2.3 Pillar 3: Enabling Technologies

Pillar 3 focuses on Enabling Technologies, and more specific on 'Enabling technologies and approaches in order to fundamentally understand, monitor and improve molecules in Chemistry for Life. This pillar links Pillar 1 (Health) and Pillar 2 (Food and Nutrition), as well as all Life Science technologies of the KIA Key Technologies. The aim is to create a deeper understanding of the building blocks of life and developing enabling technologies while providing valuable input for understanding, monitoring and improving health(care), food security and eventually other sectors such as biomaterials, circular economy and sustainable energy. Also contributing to the KIA Health & Care with the mission that by 2040, all Dutch citizens will live at least five years longer in good health.

2.3.1 Enabling Technologies Task 1: (Bio)chemical processes from molecule to organism

Living cells are biochemical reaction factories. Many of the basic elements of enzymatic reactions have been studied in detail for isolated systems but how these integrate in large networks is still mysterious. We aim to understand how biochemical reactions occur in living cells. To advance on these challenges, a basic understanding of cellular systems at the molecular level is required, in particular with respect to functional heterogeneity among individual cells and the dynamics of complex networks. With this knowledge we aim to engineer cells and cell like entities such that they fulfill specific tasks, use the molecular parts of cells to create new materials or even build designer cells and build a synthetic cell from individual parts.

To achieve this:

The cell with all of its constituents forms the basic element of life. Our knowledge on these systems provides the foundation for advanced applications ranging from medicine and health, food, energy and materials. This task is focused on a fundamental understanding of the molecular structures, dynamics and interactions that define biological functions of individual living cells, including interactions with the environment and the heterogeneity within cell populations.

Specific steps required present-2040:

- Understanding of complex cellular networks with an emphasis on dynamics.
- Development and use of advanced methods in molecular imaging (e.g. use biosensors, super resolution microscopy), ribosomal profiling, analytical chemistry, mass spectrometry, computational and AI-based approaches to map cellular networks and their dynamics, and employ molecular biology, optobiology and chemical biology to perturb network processes and identify relevant physiological response.
- Modelling of the network dynamics to allow for the accurate prediction of the behaviour of sub-cellular processes, cells and tissues under defined conditions taking heterogeneity into account.
- Quantitative description of biochemical processes in individual cells.
- Elucidate the molecular basis of cellular heterogeneity by large scale of single cell 'omics' such as DNA-, RNA-, protein- and metabolite-analysis.
- Understand, at the single cell level, processes such as cellular differentiation, specialization, and responses to external factors such as drugs. Apply simulations and advanced computational methods to achieve this predictive understanding and progress to more complex systems (tissues, organisms).

Milestones:

- Insight in the impact of the heterogeneity of proteins and protein complexes on cellular networks
- Influence of heterogeneity in the dynamics of bio-molecular networks and on the robustness of systems.
- Impact of (epi-) genomics on the heterogeneity of individual cells, cellular dynamics, differentiation and interactions with the environment.
- Utilize the knowledge on network dynamics and cellular heterogeneity to tackle main societal challenges.

Expected result present-2040:

Scientific/technological goal:

- An understanding of the dynamics of networks and cellular heterogeneity will provide a deeper understanding of the collective behaviour of cells such as in cell populations, tissue and organs. Develop predictive models for system robustness. Develop novel chemical methodologies and smart formulation for more sustained API manufacturing.

Industrial end goal:

- Application of single cell technologies in the regulation and functioning of processes such as in plant breeding, antibiotics resistance (persistence), the productivity of micro-organisms in biotechnological applications, and bio-inspired materials.

Societal goal:

- By studying individual processes, important insights will be obtained in the mechanism of aging, cellular differentiation and disease (for instance, the onset of cancer development and neurodegenerative disease), as well as in medical treatments that affect the behaviour of individual cells ultimately contributing to the central mission of the KIA Health & Care. Increased health with a smaller environmental impact.

2.3.2 Enabling Technologies Task 2: Engineering of molecules and cells

During the last decades, technological advances enable the modification of biological materials at an advanced level. This involves DNA reprogramming and substitution, control of protein production but also the reconstitution of protein complexes, membranes and other macromolecular structures such as the cytoskeleton which links to the Advanced Materials cluster within the KIA Key technologies. Also, synthetic parts with self- assembling properties can be generated such as complex DNA structures (DNA origami) and membranes. Further advances in reconstitution and synthesis methods will enable more directed modifications and the construction of hybrid systems. This technological advance will enable and further the directed design and construction of cells. The proposal is to add networked capabilities to cells to increase their functionality; to construct a minimal cell that is able to perform a basic level of gene regulation, homeostasis with its environment and that even can divide; to build a functional organelle; and to create functionally interacting cellular systems such as an “Organ- on- a-Chip”. In addition, cell-like entities with coupled complex functions can find many applications in medicine like cell and gene therapies and mRNA vaccines and in material development; in smart diagnostics to collect information on the chemical status in a body and report back via AI-based approaches or non-invasive imaging for personalised medicine, to prepare dynamic self-assembling structures, to promote complex series of catalytic steps, to deliver therapeutic agents to specific (sub)tissue locations with variable controlled local release or modified local reactions, to stimulate and participate in tissue repair and to make medicines production clean and sustainable.

To achieve this:

In order to build functional cells and cellular systems both a bottom-up and top-down approach is needed. In the bottom-up approach we have to identify the chemical components and their relevant interaction networks to generate systems with increasing complexity and predictable function. In the top-down approach, existing cells and cellular systems are exploited and modified to re-program their function for specific tasks. This also involves harnessing cell heterogeneity for complex functions including mimicking organs.

Specific steps required present-2040:

- Development of synthetic and chemical biology, bottom up.
- Development of a synthetic cell from building blocks capable of performing basic reactions such as lipid biosynthesis, gene regulation, protein synthesis, ion homeostasis and division. Identify the minimal requirements to generate an autonomously operating system based on a minimal synthetic genome.
- Development of synthetic and chemical biology, top down.
- Development of minimal cells. Identify the requirements to speed up genome editing for genome minimization and the introduction of complex multi component biosynthetic pathways and specialized cell factories.
- Development of multicellular biological model systems such as “Organ-on-a-Chip”. Identify the requirements to generate a robust system for high throughput screening.

- Development of synthetic microbial communities for specific tasks in bioremediation, biobased fuels, food and health.

Milestones:

- Multidisciplinary virtual centre of synthetic biology.
- Minimal cells that conduct specific biochemical reactions in a robust manner and that can be used in applications related to healthcare, personalised medicine, smart diagnostics, bioenergy, biomaterials, sustainable chemical production.
- Synthetic cell that in a controlled manner carries out basic biochemical reactions and that can replicate.
- Synthetic cells with diagnostics or drug delivery functions.
- “Organ-on-a-Chip” modules that can be used as a disease specific screening platform.
- Synthetic microbial communities to support the gut microbiome.

Expected result present-2040:

Scientific/technological goal:

- Assembly of biochemical reactions into functional cellular concepts up to the creation of a minimal functional cell.

Industrial end goal:

- Designer minimal cells for application and production in bioenergy, biomaterial and (bio)chemical production which supports the missions as formulated in the KIA LWV and the KIA Circular Economy and to the cluster Advanced Materials in the KIA Key Technologies; Tailor made platforms for high throughput drug screening.

Societal goal:

- Alternative systems to replace animal testing in the development and clinical testing of medicines. Cell like entities as smart diagnostic and therapeutic agents, improving health and healthcare. Thus supporting the central mission of the KIA Health & Care.

2.3.3 Enabling Technologies Task 3: Applying Green Chemistry Principles

Applying Green Chemistry Principles, modern catalytic and/or energy friendly production methods will aid sustainable production of medicines, cosmetics and other consumer products and will result replacement of solvents and reagents by environmentally friendly alternatives. Also, smarter targeted and/or controlled release formulations will reduce the use of APIs and reduce the environmental impact of unused or insufficiently active medication. In addition to the development of new sustainable chemical processes, there is also a need for new catalytic approaches that allow remediation of polluting chemicals that are already in the environment.

To achieve this:

The development and use of innovative technologies like green solvents, biocatalysis, and renewable energy integration should be encouraged. Achieving green chemistry principles involves designing chemical products and processes that reduce or eliminate the use and generation of hazardous substances. By applying green chemistry principles, the environmental footprint can be reduced while maintaining or even improving the efficiency and cost-effectiveness of production processes. Also, new (bio)chemical processes are needed to solve environmental problems, such as methods to degrade persistent pollutants such as (nano/micro)plastics, PFAS, pharmaceuticals and difficult-to-degrade food-derived compounds.

Specific steps required present-2040:

- Processes need to be developed to maximize the incorporation of all materials used in the process into the final product.
- Development of real-time monitoring methods that can aid in minimizing waste.
- Development of chemicals that are effective but have low toxicity to humans and the environment. In addition, it should be considered that the product can degrade into harmless products.
- Development of synthesis methods that use safer substances while avoiding the use of toxic materials by selecting alternative reagents and solvents.
- Processes need to be developed that allow the degradation of pollutants into non-harmful compounds.

Milestones:

- Achieving a chemical industry where waste products are systematically repurposed or regenerated.
- The replacement of toxic chemicals with safe and 100% renewable materials and the widespread use of biodegradable catalysts that can be reused multiple times without losing effectiveness.
- Bio-manufacturing platforms that produce high-value chemicals and materials entirely through biological processes, with minimal environmental impact.
- The elimination of hazardous substances in the environment and consumer products, with green alternatives becoming the default option.

Expected result present-2040:

Scientific/technological goal:

- To design chemical products and processes that reduce or eliminate the use and generation of hazardous substances.

Industrial end goal:

- To create a sustainable and environmentally responsible chemical industry, which involves the complete integration of green chemistry principles into every aspect of chemical production, from the design of molecules to the disposal of end products.

Societal goal:

- To protect and enhance human health and the environment by fostering a sustainable society in which the production and use of chemicals are safe, responsible, and beneficial for all.

2.3.4 Enabling Technologies Task 4: Development of analytical tools

Analytical tools in health, food, and nutrition are essential for assessing the quality, safety, and nutritional content of food products, as well as for monitoring health biomarkers in humans. These tools range from laboratory-based techniques to portable devices and software applications. Further developments will significantly enhance our ability to assess, monitor, and improve food quality, nutritional content, and health outcomes. These advancements will be driven by innovations in technology, data analysis, and a deeper understanding of biological systems.

To achieve this:

Emerging technologies should be leveraged, such as AI, big data analysis and nanotechnology. Sensor technology should be further developed, such as multiplex detection, miniaturization and non-invasive or minimally invasive analytical tools, such as wearable sensors or breath analyzers, that can monitor health indicators without the need for blood draws or other invasive procedures. Analytical tools that can provide personalized insights based on an individual's genetic makeup, microbiome, and metabolic profile should be developed. These tools can help create customized dietary plans and health interventions that are more effective for individual needs. These analytical tools can be integrated with mobile health apps and wearables to provide real-time feedback on diet and health.

Specific steps required present-2040:

- Development of analytical tools for health, food and nutrition in general.
- Development of multiplex and wearable sensors that can simultaneously detect multiple targets, such as nutrients, contaminants, and health biomarkers.
- Development of analytical tools and processes that minimize the use of hazardous substances and reduce waste.
- Integration of AI and machine learning into analytical tools to enhance data analysis, pattern recognition, and predictive modelling to help interpret complex datasets, optimize processes, and make real-time decisions in food quality and health monitoring.

Milestones:

- Development of analytical tools for assessing, monitoring, and improving food quality, nutritional content, and health outcomes that ultimately lead to a healthier and more sustainable future.
- Analytical tools that contribute to sustainable practices in food production and healthcare.
- Integration of analytical tools with AI and big data analysis to provide comprehensive insights into the relationships between diet, nutrition, and health.

Expected result present-2040:

Scientific/technological goal:

- Advancement of understanding of biological processes, improving the accuracy and efficiency of measurements, and enabling new discoveries that can lead to better health outcomes and food quality.

Industrial end goal:

- Enhancing the efficiency, quality, safety, and profitability in nutrition, food production and health.

Societal goal:

- Improving public health, enhancing quality of life, and fostering sustainable development.