ChemistryNL Roadmaps 2020-2023

Index

Useful links:

KIA Energy transition and Sustainability In which the sub KIA Circular Economy KIA Health & Care

KIA LWV

KIA Security

KIA Key Technologies

KIA Social earning capacity

INTRODUCTION

This is the roadmap of ChemistryNL to succesful public-private partnerships. PPPs in the chemical sector contribute to and enable the socio-economic missions. They also form a large subset of the defined key technologies, even beyond those classically characterized as ‘chemical technologies’. This roadmap has two functions. Firstly, it describes the ambitions and benefits of the technological disciplines within the sector. Successfully tackling socio-economic challenges (as described in the missions addressed by the mission-driven topsector and innovation policy, MTIB) needs enabling sciences and industries. By maintaining and advancing innovation in these structural elements we can tackle our mission from strength. Secondly, the roadmap is a guide for our innovators - in public knowledge institutions, corporate R&D and SMEs. Often starting from a discipline, they may need guidance towards the connection with the Dutch mission driven innovation policy. Which programs (MMIPs), which calls do I need to connect to? Where do find ground for connection? How can I speed up my (company’s) foreseen innovation?

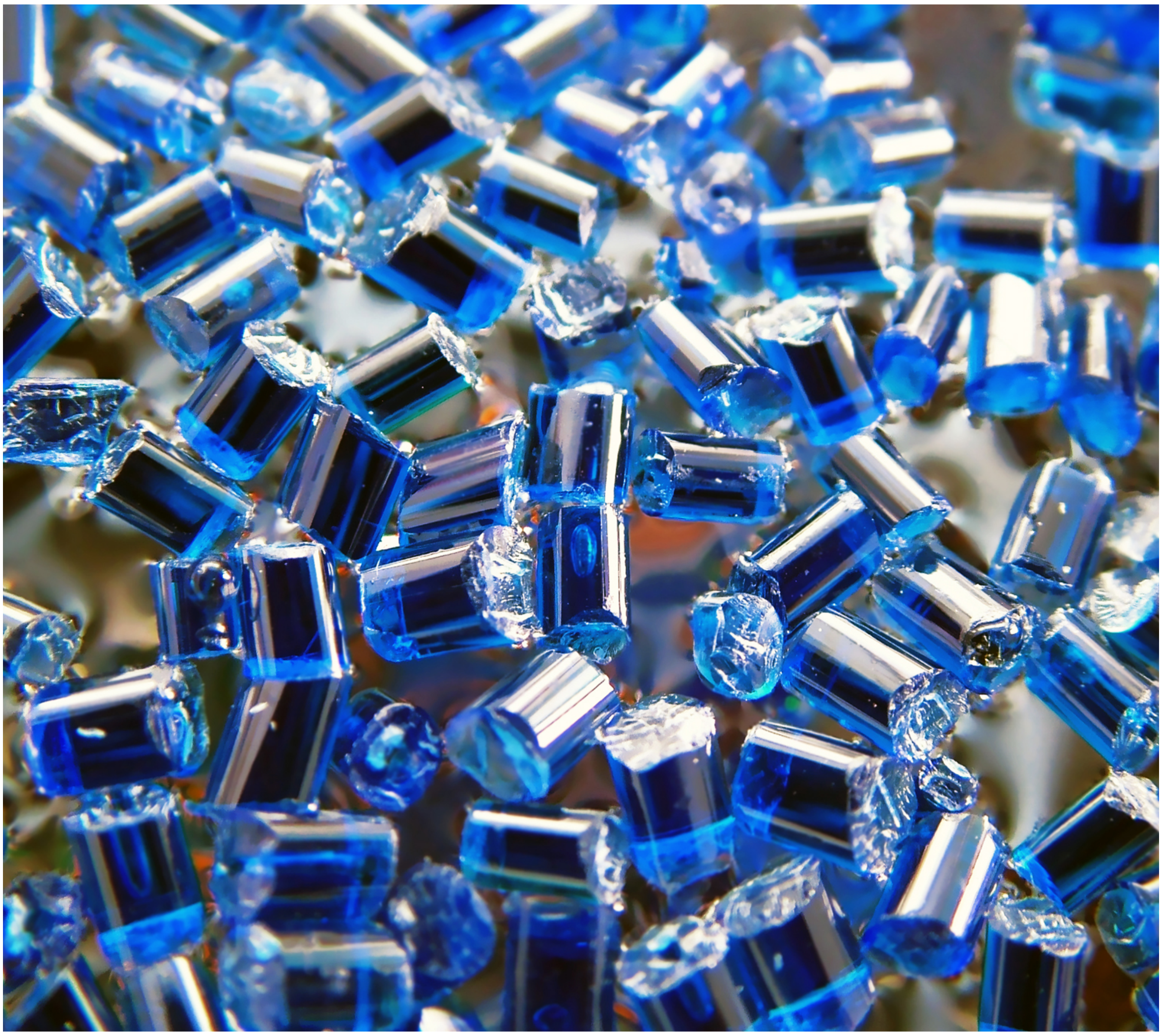
Serving these two functions this roadmap is the synthesis of four roadmaps, which originate from our four “sub-disciplinary” program councils: Chemistry of Advanced Materials; Chemical Conversion, Process Technology & Synthesis; Chemistry of Life; Chemical Sensing & Enabling Technologies (formerly known as Chemical Nanotechnology and Devices) –the coucils also being the “communities in which the natural first point of interaction around chemical technologies occurs. If we start new public/private projects and programs within the realm of chemistry (for instance with PPP-premium, this document serves as the framework to which our councils validate the fit. It also provides the anchors for monitoring the “portfolio” of PPPs for research and innovation in the topsector Chemistry. In addition, when new plans are reviewed in connection with a mission agenda or key-technology agenda, we can also map and register them as a contribution to one or more of our roadmaps.

ChemistryNL

To guide you through the landscape of roadmaps and KIA's check out the a quick guide to the connection between the mains tasks of each roadmap with the national mission and key technology KIAs.

	Energy Transition and Sustainability			Agriculture, water and food	Health and Healthcare	Security	Key Technologies	Societal earning capacity
ChemistryNL Roadmap 	Climate and Energy (IKIA) *in particular Mission C "Industry"*	Circular Economy	Future Mobilitysystems	7 missions	4 missions	8 missions	Key technnology (ST) clusters: ChemTech, AdvMat, DigTech, EngFabTech, LifesciTech, NanoTech, PhotoTech, QanTech	3 tracks
Chemistry of Advanced Materials							AdvMat; ChemTech; NanoTech	
Chemistry of Life							LifeSciTech, ChemTech	
Chemical Conversion, Process Technology & Synthesis							ChemTech, EngFabTech	
Chemical Sensing & Enabling Technologies							ChemTech, DigTech, EngFabTech, Phototech, LifesciTech, NanoTech	

Roadmap
Chemistry of Advanced Materials



Inhoud

Executive summary

Artificial materials are the cornerstone of our global society. Progress in the field of materials chemistry has enabled numerous new technologies and applications ever since the Stone Age, and will continue to do so in the coming decades. The Netherlands has a very strong position in various fields of advanced materials, and has a high ambition level for extending this position; in the period 2030-2040, The Netherlands will have settled its name globally as “rational material design” technology provider for high value-added, sustainable materials and clean energy materials. In keeping with this long-term ambition level, the emphasis of materials chemistry research on the short term should be on mechanistic insight to be obtained for each of a plethora of desired functionalities and on the medium to long term on moving from increasing insight and understanding towards rational material design capabilities and implementation of the technologies developed. For the latter, a broader scientific foundation of (multi)functionality of materials should be developed, including experimental multiscale analysis of material structure-property relations and (predictive) modelling of formulations and properties.

The roadmap Chemistry of Advanced Materials deals with the (bio)chemical synthesis or chemical modification of materials in relation to their desired functionality. This includes organic materials, inorganic materials and hybrids. Examples of organic materials are engineering plastics and resins, and examples of inorganic materials are sol-gel metal oxides or metal borides and carbides produced via chemical vapor deposition. All activities in this field should include end-of-life considerations for the materials after use. The roadmap Chemistry of Advanced Materials has focused on three tasks: **Materials with added Functionality, Thin films and Coatings, and Materials for Sustainability**. All three tasks revolve around the key word “functionality” and prepare for a future in which advanced materials exhibit new functions, new combinations of functions, or true step-change improvements in their functions. Under the first task, the functionality is defined by the continuum (or “bulk”) intrinsic properties of the materials, whereas surface effects dominate those properties under the second task. Under the third task, the functionality is related to sustainability. Either directly, when the material itself is made in a sustainable way, or indirectly, when the material enables sustainable energy harvesting or energy storage, reduction of energy consumption or requiring less (scarce) resources for production. Intrinsic design of advanced materials based on, or allowing for, circular economy or replacement of advanced materials with more sustainable alternatives is bridging task 3 with tasks 1 and 2. Of course, these three tasks are not mutually exclusive. The overall ambitions of each task and the specific steps that should be taken between now and 2050 are summarized in the tables below each theme.

This roadmap on the chemistry of advanced materials is mainly sustained by the Topsector Chemistry roadmap on Making Sustainable Chemical Products and the **TKI Biobased Economy**, by providing sustainable raw materials and (catalytic) technology for control of conversion of these raw materials into advanced materials. In turn, the major beneficiaries of this roadmap are in the Topsector Chemistry roadmaps on Chemistry of Life (Biomedical Materials) and on Chemical Sensing and Enabling Technologies, as well as in the topsectors **High-Tech Systems and Materials, Energy** and **Water** for applications of these advanced materials. These applications are fully in line with the Horizon Europe themes.

ChemistryNL

	Energy Transition and Sustainability			Agriculture, water and food	Health and Healthcare	Security	Key Technologies	Societal earning capacity
ChemistryNL Roadmap	Climate and Energy (IKIA) *in particular Mission C "Industry"*	Circular Economy	Future Mobilitysystems	7 missions	4 missions	8 missions	Key technnology (ST) clusters: ChemTech, AdvMat, DigTech, EngFabTech, LifesciTech, NanoTech, PhotoTech, QanTech	3 tracks
Chemistry of Advanced Materials							AdvMat; ChemTech; NanoTech	
Materials with Added Functionality	Advanced building materials in MMIP3 Composite materials for transportation in MMIP9		Composites for ships and airplanes		Sensing materials for prevention in mission I/II	High strenght materials and sensor materials in mission 2	Sensing materials in ST3 Photonic and photovoltaic materials in ST4 Nanomaterials in ST8	
Thin Films and Coatings	Wind turbine blade coatings in MMIP1 Coatings for transportation in MMIP9		Coatings for ships and airplanes	Use of protective films for food in mission D	Biostable/resorbable and antimicrobial materials in mission III	Coatings for low detection in mission 2	Advanced materials in ST5 Biostable/resorbable materials in ST6	
Materials for Sustainability	Photovoltaic materials in MMIP2 Thermoelectric and magnetocaloric materials in MMIP4 Redesign of materials for circularity in MMIP6 Battery materials in MMIP8	Design for circularity in materials		Use of bio-based materials in mission A/B		Materials for additive manufacturing in mission 6	Materials for additive manufacturing in ST3	

1 Introduction

Mastering materials has paved the progress of mankind ever since the Stone Age. Now, thousands of years later, artificial materials are the cornerstone of our global society. Materials are present everywhere in our daily life in buildings, furniture, clothes, transportation, and electronic applications but likewise they are part of food and healthcare products, diagnostics, and biomaterials. Progress in the field of materials chemistry has enabled numerous new technologies and applications in this period. Recent examples are found in composite materials for aerospace, smart phones and tablets, energy efficient lighting, solar energy conversion, self-cleaning coatings and materials, and rechargeable batteries. Next to these examples, materials chemistry has also substantially contributed to developments in food packaging, in biobased materials, soft robotics, and in enabling regenerative medicine and making artificial skin and other tissues or even organs.

Advanced Materials in the context of the roadmap are defined as materials that offer superior levels of performance or additional features and added value compared to existing materials for a specific application. However, one can also argue that Advanced Materials are those of which the true relevance still needs to be firmly established, but that offer, at present, new exciting opportunities in terms of properties or applications. In this sense also known materials that can be processed via innovative techniques, such bottom-up self-assembly or top-down methods such as additive manufacturing, should be designated as advanced.

Advanced Materials do not exist without materials chemistry. Chemists are able to design materials and control their structure from the atomic and nanometer scale up to macroscopic dimensions. *Advanced materials chemistry* involves assembling atoms or molecules in a controlled fashion, covering microscopic, mesoscopic, and macroscopic dimensions. Whether this control is achieved by sophisticated (macro)molecular synthesis, directed crystallization or deposition or by advanced processing, understanding the interactions across all of these dimensions is key. Theory and computational methods will increasingly be used to guide materials discovery. Controlling matter and understanding its behavior over up to ten orders of length scales is a unique aspect of all modern materials: from stainless steel to specialty polymers, and from concrete to membranes for artificial kidneys. Advanced material science unites chemistry with aspects of physics, biology and engineering to understand and control materials properties and their interplay with artificial and living systems.

Advanced Materials is an internationally vibrant field of research and new developments. Novel materials with new properties, being organic, inorganic, biobased or hybrid in nature, are being discovered almost on a daily basis and are revolutionizing our society. Super strong polymer fibers, new carbon allotropes such as carbon nanotubes and graphene, gallium nitride for energy efficient lighting, and new perovskite semiconductors for solar cells and biodegradable plastics are just a few examples of materials that were unknown 25 years ago but are expected to change our world. The whole life cycle of these new and technologically advanced materials needs to be taken into account to provide solutions to the societal challenges of 21st century in areas of energy, water, health, environment, sustainability, transport, and food. New materials will improve our planet and the wellbeing of its people.

The Netherlands has a very strong position in various fields of advanced materials. Many excellent academic research groups, prominent research institutes, world leading multinationals, and innovative SMEs and start-up companies exist. The Netherlands can strengthen its position as a key player in the area of Advanced Materials, but contributing to true innovation requires focus and collaboration between all stakeholders. This roadmap provides a framework for research and innovation in Advanced Materials in The Netherlands as part of the Top Sector Chemistry in three main fields related to societal challenges:

1. **Materials with added functionality**, related to Energy, Health, Mobility, Construction, Environment and Climate
2. **Thin films and coatings**, related to Food security, Energy, Wellbeing and Health
3. **Materials for sustainability**, related to Resource efficiency, Climate, Energy, Wellbeing and Health

2. Overview of themes

In this chapter, we describe the grouping of advanced materials research in relation to the societal needs we see for the coming decades. A growing population (aspiring higher living standards) and the rapid depletion of natural resources pose future challenges. Material science is instrumental in finding solutions. In the prioritization of research areas that will be addressed within the Chemistry of Advanced Materials program of the top sector Chemistry the societal relevance is important, as well as the excellence of materials research in The Netherlands in specific areas. Both existing and future opportunities for economic activities related to these materials research areas have resulted in the selection of three main tasks:

1) **Materials with added functionality**. Our society needs materials "to do more with less": less weight but higher strength or performance, and able to exhibit multiple functionalities too. Materials combining multiple functionalities ("smarter" materials) provide an added societal and economic value.
2) **Thin films and coatings**. In thin films and coatings, the effects of the surface on the properties, as well as the functionality that the surface properties bring in the use of the material, add to the complex needs in society for "smart surfaces".
3) **Materials for sustainability**. Doing more with less should ultimately result in a smaller footprint of material use on our planet and less dependency on geopolitical developments. The resources of fossil fuel and raw materials are dwindling, and climate change forces society to alter the sourcing of its materials, and use materials for saving energy, sustainable production of energy and reduce, replace or recycle the use of scarce elements.

We have defined these tasks based on a ***priority analysis*** of the factors described in the following paragraphs (contribution to People, Planet and Profit, fit with Horizon Europe overarching themes, fit with the Dutch landscape, and technology gaps), with the aim of being as ***inclusive*** as possible for Dutch universities, institutes and companies, and allowing for the highest possible ***thematic overlap*** with other Topsector Chemie roadmaps (e.g. Nanotechnology and Devices, Chemical Conversion), other Top sectors (e.g. High Tech Systems and Materials, Energy, Life Sciences & Health, AgriFood) and existing vision documents.[1]

The tasks have an excellent fit excellently to with the mission driven research agenda of The Netherlands. Chemistry of advanced materials can be found as cornerstones of IKIA and KIA CE of the mission "Energietransitie en Duurzaamheid". For instance, photovoltaic coatings and materials in MMIP2, thermolectric and magnetocaloric materials in MMIP4, redesign of materials for circularity in MMIP6, development of battery materials in MMIP8 and composite materials and coating for transportation in MMIP9 cannot be developed without strong input from the academic and industrial groups operating in the field of chemistry of advanced materials. Also many goals of the missions of "Landbouw, water, voedsel", "Gezondheid en zorg" and "Veiligheid" cannot be achieved without strong input from this sector. The key enabling technology "Avdanced Materials" (ST5) and all related research questions resemble the three tasks outlined here and are in fact based on this roadmap. Also other key enabling technologies heavily rely on materials development such as "Chemical Technologies" –ST1, "Engineering and Fabrication Technologies" –ST3, "Photonics and Light Technologies" –ST4, "Energy Storage Materials" –ST5, "Nanotechnologies" –ST8. Long term programs defined in the scope of these key enabling technologies such as 73 MJP –"Soft Advanced Materials" and 82 MJP –"Materialen –made in Holland" will be potential drivers to develop the research agenda in this roadmap.

All three tasks revolve around the key word "functionality". Every material has a specific purpose for its use, based on one or more implicit functions it has to fulfill. For example, a 'simple' coating on a metal bridge combines two essential functions: to protect (the bridge, from corrosion) and to decorate (appealing look). Or a food package that protects the food from getting dirty, but also increases shelf life. In that respect, there are no (current or future) materials that are not functional. However, a future can be envisioned in which advanced materials exhibit new functions, new combinations of functions, or true step-change improvements in their functions. For example, when the coating on the bridge can last 40 years instead of 15, can also sense and signal stresses, or be self-cleaning, it offers additional functionality. Or the food

[1] Vision Paper 2025 Chemistry and Physics (commissie Dijkgraaf)
Catalysis - Key to a Sustainable Future (Science and technology Roadmap Catalysis 2015)
Nationale Agenda Materialen-Accelerating Materials Technologies (MaterialenNL platform2021)

packaging material that also signals increased bacterial activity. We have tried to capture this under the term "added functionality", where "added" refers to the newness introduced in comparison to the currently known uses of the materials.

Under the first task, the functionality is defined by the continuum (or "bulk") intrinsic properties of the materials, whereas surface effects dominate those properties under the second task. Examples of the first include low-weight car parts or construction materials, biomedical implants, whereas membranes, specialty packaging, antimicrobial coatings and thin-film sensors are examples of the second. Under the third task, the functionality is related to sustainability. Either directly, when the material itself is made in a sustainable way, or indirectly, when the material enables sustainable energy harvesting or energy storage, reduction of energy consumption or requiring less (scarce) resources for production. Intrinsic design of advanced materials based on, or allowing for, circular economy or replacement of advanced materials with more sustainable alternatives is bridging task 3 with tasks 1 and 2. Of course, these three tasks are not mutually exclusive, nor meant to be. It is well possible (and well accepted) that certain innovative ideas can find connections with all three simultaneously.

Making, characterizing, understanding, and modeling new advanced materials requires multiple key enabling technologies. We are not including them as separate tasks in this roadmap, but still want to emphasize their importance. Making materials requires novel advanced synthesis techniques (e.g. new catalysts of polymerization methods), production methods like high throughput synthesis and manufacturing and processing techniques, such as for instance advanced lithographic processes or additive manufacturing. Characterizing materials with multiple added functionalities for instance requires novel techniques to measure these functionalities in situ and in a correlated fashion. To test whether intended functions are retained under realistic (in operando) conditions, we need more in-situ (realistic) characterization. To connect across length scales, we need technology for higher resolution and multi-scale characterization. Theoretical approaches and artificial intelligence will in the future play a more important role in predicting materials properties, designing de novo materials and discovering new mechanisms beyond intuitions. In addition, big data generated by modern experimental and computational techniques is becoming more readily available, data-driven or machine learning (ML) methods will open new and exciting pathways for the discovery and rational design of materials. These new enabling technologies can even drive the development of new materials themselves, such as materials that can serve as multi-modal probes (EM, light microscopy, X-ray and neutron scattering, NMR) or materials with in-built sensors such as polymers that report the local stress. Importantly, materials research requires easy access to advanced characterization facilities such as advanced HR TEM, X-ray and neutron scattering, (solid state) NMR, light microscopy and high-performance computing.

In the next chapter, we will describe in more detail what functions can be envisioned under these challenge themes, while we depict for each the Dutch profitability balance: with the available know how infrastructure and manufacturing capabilities in the Netherlands. Are we globally competitive? Can we develop the material/technology and extract the value in the Netherlands (delivering jobs in R&D as well as full scale production, a full footprint in the Dutch economy)? Or can the technology (only) be patented and valorized via worldwide licensing of Dutch technology? Which areas can be identified for which the position in The Netherlands is not strong yet but have the potential to develop if we invest?

2.1 Materials with added functionality

Introduction

For many applications, the demands on materials become higher, while at the same time the market is very competitive and global, which puts a lot of focus on reducing costs. A number of successful examples from the past have shown that the Dutch industry, together with knowledge institutes (*e.g.* Dutch Polymer Institute, Materials Innovation Institute, AMOLF, DIFFER), can pave the way in the advanced polymer, nano and hybrid (metal) materials and composites arena by using a systems approach. This implies that a strong link is needed between the chemistry of **making optimized advanced materials** and **processing with cost-efficient technologies**, so **the right application domains** can be targeted. This especially holds for materials enhancing circular economy and hydrogen mobility (e.g. aerospace and automotive). In general, it can be stated that the need for new metallic, ceramic, (bio)polymeric, and composite/hybrid light-weight materials is growing rapidly. Classic material selection approaches will no longer work. Well-known Ashby material selection charts, as shown in Figure 2.1, are an initial start, but new applications for the above-mentioned industries can only be realized when new materials become available that offer a combination of properties, e.g. they can be used as a structural load bearing component while also offering additional functionalities such as self-healing, sensing or actuation. Such new materials ideally have to be produced, processed and recycled in a sustainable manner. Value should be created according to a 'more for less' philosophy. Reduce the weight of a design but add functionality. The value will be in price per economic value added rather than producing kilograms.

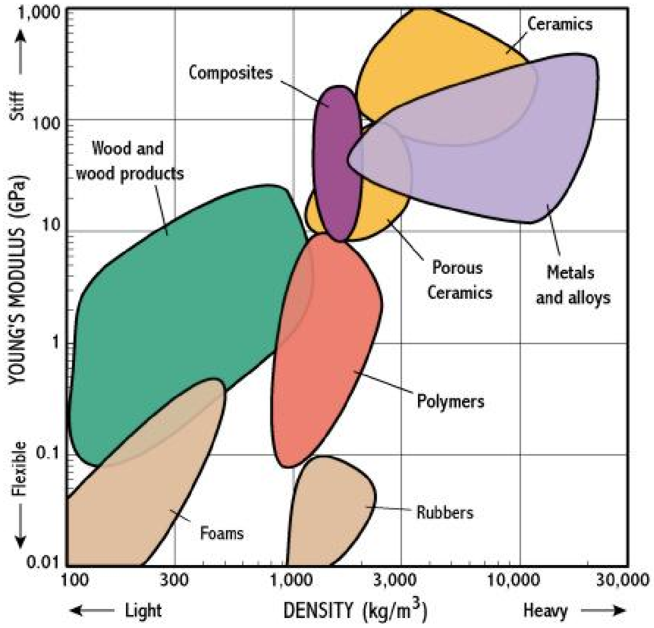


Figure 2.1 *Material selection chart as introduced by Michael Ashby. Material properties, in this case density (kg/m^3) vs. Young's modulus (GPa), are plotted in pairs on a chart, allowing the user to find the right material for the right job.* (Ashby, Michael (1999). *Materials Selection in Mechanical Design (3rd edition ed.).* Burlington, Massachusetts: Butterworth-Heinemann. ISBN 0-7506-4357-9. Cf: www-materials.eng.cam.ac.uk/mpsite/physics/str-tough_article/ of http://store.elsevier.com/Materials-Selection-in-Mechanical-Design/Michael-Ashby/isbn-9780080468648/)

Also the trend towards more personalization in products with high quality-of-life requires a different mindset toward the design and processing of new functional materials with on the one hand more automated processes, while on the other hand allowing organic materials, based on "molecules" (mainly polymers), as their design and production from raw materials (petro- or biobased) depends highly on manufacturing capabilities for which we refer to the Roadmap Making Sustainable Chemical Products.

Tasks

Description of the task and the relevance for society, industry and science

Advanced materials are characterized by their high degree of functionality. Society has always been looking for stronger, faster, and thinner, more efficient and lighter, say 'superior' materials. Solutions are therefore developed based on market-pull mechanisms and science and technology play a dominant role in the development of materials that can bridge the actuality with societal desires and needs.

Solution for this task described SMART (present-2050)
Present-2025 Starting from a strong point of NL, with excellent R&D infrastructure and a good basis for public-private partnerships in material technology development, new mechanistic insights should be obtained for each of a plethora of desired functionalities (see 2.1) in e.g. functional polymers, nanocomposites, metals, and high tech materials aimed at aiding implementation of new functionalities in products in cooperation with industrial partners. Also, more insight will be obtained on the sustainable recyclability of materials with added functionalities where the added functionality is being maintained. From a fundamental science perspective, specific functionalities should be fully understood, also in relation to each other and to other material requirements. Basic research in emerging classes of advanced materials is strengthened as a seedling for novel applications that we cannot think of yet. The entrepreneurial climate, as well as strong "designer material" knowledge base combined with the know-how how to design and manufacture with those materials, will allow the growth of start-up companies (e.g. Xilloc Medical and Chemelot InSciTe).
2025-2035 Moving from increasing insight and understanding towards rational material design capabilities, a broader scientific foundation of functionality of materials is developed, including (predictive) modelling of formulations and properties and efficient recycling. Several new technology platforms are expected that make NL an attractive manufacturing area as price per kilogram will be replaced by price per economic value added. This will be in support to typical EU industries like agricultural, car manufacturing, medical, high tech, and energy related industries and in full support of the ageing population.
2035-2050 Three decades from now, NL will have settled its name as "rational material design" technology provider for high value-added materials, and clean energy materials, based on its knowledge infrastructure and IP position, and its demonstrated infrastructure for introduction of new technologies to the market.

What existing competences, technologies, knowledge contribute to this task?
Traditionally, the Netherlands has a strong and internationally renowned basis in the development of sophisticated functional materials. This is due to the presence of a variety of companies in the areas of materials, and devices, as well as a well-developed R&D infrastructure (TOP institutes and technology campus models). This ranges from polymers to computer chips and from bio-medical applications to car manufacturing. The Netherlands offers state of the art Large-Scale Research Facilities (organized via the National Roadmap) for characterizing materials properties, including free-electron lasers (FELIX, Nijmegen), neutron scattering (Oyster, Delft), electron nanoscopy (NeCEN, Leiden), and nuclear magnetic resonance (Utrecht).

What additional competences, technologies, knowledge do we need?
Investment in the areas of bottom-up micro-meso-macro scale morphology analytics and control of (bio)polymers and/or inorganic particles (nanometer – micrometer size), nanotechnology/nanoscience and nature inspired self-assembly is crucial for the development of advanced materials. This area is highly multidisciplinary in nature and requires intimate collaboration between chemistry, physics, life sciences, and bioengineering, with a strong input from rapidly advancing analytic techniques (allowing multimodal functionality and morphology characterization on the nanoscale). In addition, integration of multiple length scales in the research is crucial to understand how functional properties on the nanoscale affect functionalities on larger length scales and can be implemented in new products. This needs to be supported by modelling and computational chemistry on all these different length scales (micro: Molecular Dynamics, meso: coarse graining, macro: finite elements); a particularly outstanding challenge is to connect models at different scales and data-driven modeling in order to achieve predictive frameworks that can guide new materials developments. In addition, knowledge on the manufacturing of materials with added functionalities needs to be built up, for instance in rapidly growing application areas such as additive manufacturing.

Designing materials with the right functionality
In many industries, e.g. automotive, aeronautics, electronics and construction, the driver for innovation is weight and cost reduction together with higher demands on the material properties in terms of thermal, mechanical and chemical properties. In said applications engineers/designers use materials that are typically optimized to fulfill one specific task or one specific function.

In this context, functionality can be defined as:

1- **Mechanical** (e.g. strength, stiffness, flexibility, fatigue or impact stability)
2- **Chemical** (e.g. chemical stability, biocompatibility, catalytic, photoconversion)
3- **Physical** (e.g. thermal and electrical conductivity, magnetic, piezoelectric, optical)
4- **Biological** (e.g. cytocompatibility, antibacterial, bioinstructive cues)

A - Traditional materials

Over the years, chemists and material scientists have designed and optimized materials for specific applications, e.g. metals for high temperature engine parts, ceramic coatings for high high-temperature turbine coatings and polymers for ductile/light-weight packing materials. Step-changes are definitely possible in extending the current property portfolio, but the limits of traditional materials have been or will be reached soon. This can be achieved by chemical structure and processing optimization, e.g. polyethylene can be processed into high modulus/high strength yarns. Optimizing the chemistry (catalysis and polymerization conditions) and processing has the potential to further improve the mechanical properties of PE-based yarns by a few percent. Aluminum, as another example, is an alloy and has now been optimized with respect to strength and ductility. In this case, alloy design and processing are expected to result in an overall improvement of a few percent at best. For steel, on the other hand, several issues need to be resolved. Understanding fatigue behavior, improve corrosion stability and how to improve polymer (coating) adhesion on steel are still issues that need to be resolved. The same is true for continuous and non-continuous fiber-reinforced composites. The design of composite structures is sufficiently understood. However, the resin-fiber interface and processing issues need to be resolved and how composite structures fatigue over time.

B - Multi-functional materials

In order to enable the design of next generation coatings, composites, packaging, sensors, actuators etc., materials are needed that combine some level of structural integrity with one or more additional functions. Self-healing polymers or ceramics with the ability to reverse crack formation have a strong advantage over traditional construction materials. Designing multi-functional materials (MFMs) requires a multidisciplinary approach and the ability to design materials at different length scales (Å to m). MFMs are often multi-component or hybrid systems. Typical building blocks include ceramics, metals and (bio)polymers. Of interest are organic/inorganic nanocomposites where the matrix offers the structural integrity and processing capability and the nanofiller introduces a second functionality, i.e. it reinforces the matrix and adds an electrical, thermal, actuating/morphing or sensing functionality. The envisioned applications could be in photovoltaics, sensors or in bulk applications such as composites. The aim is to reduce weight, add functionality, extend the life cycle and reduce maintenance costs.

C - High-Tech materials

In the high tech industry, the rapid development of new technologies often relies on research at the interface of chemistry and physics and sometimes bioengineering. An example of the latter is the leading role of the Netherlands in the area of organ-on-chip models for animal-free experiments and personalized medicine (hDMT institute). A number of startup companies are located in innovation hubs such as the Brightlands Chemelot Campus and the Leiden Bio Science Park. In addition, small scale and cheap diagnostic equipment that can be used in the home or in remote areas is a rapidly growing market. There is a strong activity in the Netherlands. Cooperation between large companies and SME's, in the biomedical field, and universities and university hospitals has been supported in several successful programs (BMM, CTMM, HTS&M). Challenges include research on the nanoscale. Bio-molecules of nm dimensions (e.g. proteins and DNA) are at the basis of diseases and (bio)chemistry now allows for the synthesis or recombinant production and the controlled self-assembly of these molecules. Future prospects in this field include:

- Control of interaction of living matter with man-made materials will allow to replace or assist dysfunctional organs beyond the traditional implants.
- Microtissue and organ-on-chip models for animal-free experiments and personalized medicine.
- Imaging using (multi-functional) nanoprobes in combination with controlled drug delivery and/or release makes a more targeted and personalized medicine possible.

Inexpensive small scale diagnostics (e.g. using lab-on-chip technology, even in combination with mobile phones) based on (nano)sensors for diagnosis at home or in remote areas is a growing area and requires a continued effort in finding new materials for more reliable and cheaper diagnosis.

Summary

Topic	Short term (-2025)	Medium term (2025-2035)	Long term (2035-2050)
Traditional materials	• Improved mechanical properties of traditional polymers (TRL6) • Understanding fatigue and improving the corrosion stability of steel (TRL3) • Insight in the resin-fiber interface for fiber reinforced composites (TRL 3) • Upscaling of self-healing polymers and ceramics (TRL 7)	• Higher strength polymers industrially produced (TRL 6) • Several insights described above (corrosion, fatigue) will lead to development of improved materials that are tested in a simulated environment (TRL 5) • Superior composites are designed based on new insights (TRL 3)	• Reinforced composites and materials with improved properties successfully introduced to market (TRL 9)
Multi-functional materials	• Development of polymers with additional functionalities (e.g. optical, magnetic, electronic, selective permeability, bioactive) (TL3) • Design of new materials for EUV lithography and for additive manufacturing (TL3) • Development of smart materials and solutions for sensors and actuators in homes and automotive (TRL 3) • Materials for higher precision positioning and improved sensitivity sensors (TRL 3) • Development of a technology platform for multiple, selective response factors (TRL 3) • Development of recycling methods for materials with added functionalities (TRL2)	• Response platform will be broadened by new concepts (TRL 3) • Sustainable recycling technologies for materials with added functionalities (TRL 5) • Sustainable recycling technologies for materials with added functionalities (TRL 5).	• New multi-functional materials successfully introduced to market (TRL 9) • Several new concepts for multi-functional materials be further developed to prototypes (TRL 7) • Sustainable recycling technologies for materials with added functionalities (TRL 7)
High-tech materials	• Design of new materials for EUV lithography and for additive manufacturing (TL3)	• Response platform will be broadened by new concepts (TRL 3) • Sustainable recycling technologies for materials with added functionalities (TRL 5).	• High tech materials proven to function in several prototypes (TRL 9) • Sustainable recycling technologies for materials with added functionalities (TRL 7)

	• Development of smart materials and solutions for sensors and actuators in homes and automotive (TRL 3) • Materials for higher precision positioning and improved sensitivity sensors (TRL 3)		
Bio-medical materials	• Control of interaction of living matter with man-made materials (TRL 3) • New platforms for theranostics (TRL 3) • Development of small scale disease diagnosis schemes (TRL 3) • Development of a technology platform for multiple, selective response factors (TRL 3)	• Selection of biomedical materials tested (TRL 5) • Sustainable recycling technologies for materials with added functionalities (TRL 5).	• Biomedical materials for diagnostics and/or controlled drug delivery in clinical trials (TRL 7) • Several new concepts for biomedical materials will be further developed to prototypes (TRL 7) • Sustainable recycling technologies for materials with added functionalities (TRL 7)

2.2 Thin films and coatings

Introduction

In addition to the challenges described for functional materials in the previous paragraph, there are specific other challenges for functional coatings and thin films , related to their surface-dominated property demands. In this task we focus on those additional functionalities, but it is clear that for a large number of applications the required thin film / coating properties also involve the continuum characteristics described earlier (mechanical, chemical, physical) as well as the dependency on the manufacturing capabilities of the (macro)"molecules" that have to constitute these functionalities.

The science in this field has made impressive progress in the past 15 years. For example, smart coatings which are switchable from IR transparent to blocking by response to external triggers such as temperature are being explored. Further development of the underlying technologies will open new opportunities.

Tasks

Description of the task and the relevance for society, industry and science

Functional coatings, thin films and membranes are of importance for a broad spectrum of applications ranging from biomedical to energy harvesting and storage. Although coatings with one or multiple passive functionalities are already known and applied, active, adaptive and even instructive systems are rare. The potential value of such systems which can adapt to their external environment or potentially even instruct biological species to perform in a certain manner, is very high. Similar considerations are valid for functional thin films and membranes. Furthermore, functional coatings, thin films and membranes should be developed to facilitate energy efficiency, harvesting and storage. This includes the development of novel, non-toxic and durable antifouling coatings for maritime applications. Additionally, membranes have the potential to become important contributors to sustainable chemical processes. Moreover, functional coatings, thin films and membranes that contribute to a circular economy should be developed, *e.g.* product related to circular packaging and reversible adhesives, and retrofit solutions to restore functionality in existing systems.

Solution for this task described SMART (present-2050)

Present-2025 The development of functional coatings, thin films and membranes should focus on following main topics: (a) the transition from coatings with one or multiple passive functionalities to active, adaptive and even instructive coatings, (b) the development of coatings, thin films and membranes tailored for energy efficiency, harvesting and storage, (c) the development of bio-instructive coatings and (d) the development of membranes for sustainable chemical processes, (e) functional coatings, thin films and membranes that contribute to a circular economy.

2025-2035 Start-up companies/SMEs in functional coatings, thin films and membranes should grow, and first demonstrators of coatings, thin films and membranes from the above mentioned categories should find their way into industry. First responsive/active biomedical systems should be industrially produced, and first bio-instructive systems should be demonstrated at TRL 5-7.

2035-2050 Three decades from now, NL will be a world leader in functional coatings, functional thin films and membrane technology and provide high value-added adaptive/active/instructive systems. Bio-instructive coatings are industrially produced, new breakthrough energy harvesting/storage concepts are developed to prototypes, and functional coatings, thin films and membranes that contribute to a circular economy should be developed, *e.g.* product related to circular packaging and reversible adhesives, are widely implemented.

What <u>existing</u> competences, technologies, knowledge contribute to this task?

Traditionally, NL has a very strong position in coatings, thin films and membrane materials, both in research institutes and industry. Advanced infrastructure allowing control down to the level of a single atomic layer, as well as characterization techniques (including large scale facilities like synchrotrons) have been established in NL (with support from programs like NanoNed and NanoNextNL) and require continued investments.

What <u>additional</u> competences, technologies, knowledge do we need?

The same needs exist here as under 2.1.1.4, but more focused on surface driven phenomena in coating, thin films and membranes. Material surface analysis and characterization on the level of such thin films has to be developed strongly (microscopy, spectroscopy, scattering, ellipsometry). Adhesion is an example of a crucial performance parameter for thin films in which fundamental understanding needs to increase substantially. Process development is required for the precision production of functional coatings, thin films and membranes, potentially involving real-time process analytical techniques. Advances in coarse grained modelling are needed to understand surface dynamics (restructuring upon different media contacts).

Designing thin films/coating materials with the right functionality

Specific surface-dominated functionalities are listed below.

1. Mechanical: adhesion of thin layers on substrates or between thin layers in multi-laminates, resistance against scratch and wear stress, switching fatigue.
2. Chemical: resistance against high-energy radiation such as UV, ozone, weather and moisture. Creation of active molecules upon absorption of high-energy radiation such as UV (photo-oxidation).
3. Physical: roughness and surface topology, optical properties of thin layers (in/outcoupling of light, matting versus gloss, reflection or antireflection), photo-active properties (photon conversion), thin layer electro-conductivity and electrical breakdown resistance. Barrier properties and perm-selectivity of thin layers and membranes.
4. Interfacial properties: solid-liquid: (super)hydrophilicity and (super)hydrophobicity, switchability. solid-solid: corrosion protection (resistance to ion migration across the buried interface), dusting. solid-cell: antimicrobial properties. solid-tissue: haemocompatibility, anti-inflammation, biostability.

A - Traditional coatings, packaging films and membranes.

Although coatings and films usually already combine different functions, we will discuss here some step changes that are still highly needed in the already known functions.

- *Anti-corrosion* is still an unsolved challenge. Advanced coatings tailored to corrosion protection of metallic substrates are of the utmost relevance to ensure reliability and long-term performance of coated parts as well as the product value of the coated materials. Durable passivation of the interface (also when damaged) remains an unmet need.
- *Barrier properties* of membranes and packaging films against most prominently oxygen, water and carbon dioxide, or even perm-selectivity are still in need of higher performance materials with tailored micro- and mesomorphology. Examples are in aluminum-free barrier packaging foils (easy to recycle, see 3.3), breathable packaging for fresh foods (water and oxygen in, carbon dioxide out), membranes for fresh water (decontamination), highly selective membranes for industrial separation processes. In addition to the above mentioned functional properties, the need for circular packaging concepts is high. This involves both the development of recycling concepts for existing commercial packaging materials, and the development of novel packaging materials according to the design-for-recycling concept.
- *Prolonged service life time* for protective and decorative coatings can result from a marked increase in UV/outdoor exposure resistance by more stable polymer design on the one hand and increased insight in stabilization mechanisms on the other. Prolonged service lifetime benefits the circular economy based on reduction of waste and less use of new materials.
- *Non-toxic and durable marine anti-fouling coatings* are highly desired in marine transport, while current technologies work only under release of heavy metals (tin, copper) or high velocities.
- *Increased use robustness of protective and decorative coatings* is a ubiquitous unmet need: car body coatings are still vulnerable to scratching, while waterborne coatings are still notoriously difficult to apply on its plastic parts without expensive pre-treatments because of loss of adhesion, membranes for energy saving separation processes have limited lifetime. Increased mechanistic insights into these mechanical properties on the micro- and mesoscale are expected to substantially increase these durability performances.

B - Active, adaptive and instructive systems The potential value of coatings which can adapt to their external environment or potentially even instruct processes that take place on their surface, is very high. Similar considerations are valid for functional thin films and membranes. Following examples illustrate potential applications of such systems:

- *Sensoring and signaling* of food packaging materials, indicating for instance heat or oxidative stress, pH change, metabolite or toxin levels, ageing or even microbial activity inside the packaging will help tremendously in prevention of food waste. But also simply monitoring the performances of thin films, coatings and membranes in situ over time without being damaged is of great desire. It will enhance the product security and safety and the response technologies will be applicable in a broad range of applications, e.g. food, water supply, construction industry, automotive, aerospace and medical equipment. A combination of responses will enhance the utility of a thin layer/coating/membrane.
- *Active ion transport* incorporated in water-permeable membranes can enable low-energy desalination devices.
- *Active scavenging or (chemo)absorption* of unwanted species (water, carbon dioxide) inside a packaging material can help to establish the ideal atmosphere for safe storage of food and medicine. All the while, packaging films become thinner, requiring less raw material to be used. This asks for a strong demand in manufacturing processes developments, e.g. multi-, micro- or even nanolayer co-extrusion processes offers enormous unexplored possibilities.
- *Coatings or films that can switch between transmission and blocking of solar infrared radiation* and *vice versa* can be applied in insulating glass units to reduce the energy consumption for heating and cooling of buildings in intermediate climates. Examples of such coatings/films are thermochromic (switch triggered by temperature), electrochromic (switch triggered by electrical stimulus) and photochromic (switch triggered by light).
- *Bio-instructive coatings* that modulate cell behaviour e.g. for engineering biofunctional surfaces of implants.

C - Coatings, thin films and membranes tailored for energy efficiency, harvesting and storage

One of the grand challenges for Europe in the coming decades will be to guarantee a sustainable supply of energy – beyond the use of fossil fuels and nuclear energy. For that purpose, efficient harvesting of renewable energy, e.g. wind or solar, and conversion into a useable form is of utmost importance. In addition, it is of vital importance to reduce the energy consumption. Both in optimizing energy harvesting/conversion en decreasing energy consumption, coatings and films play a key role. Examples include:

- *Coatings and films for photovoltaics:* light in-coupling/trapping, photon up-/down-conversion, ITO replacement, easy-to-clean, anti-dust, printable transparent conductors, passivation, improvement in life-time.
- *Coatings and films for lighting devices:* light out-coupling/extraction, photon conversion, ITO replacement, printable transparent conductors, improvement in life-time.
- *Solar control coatings for the built environment:* infrared management, switchable coatings for insulating glass units (e.g. thermochromic, electrochromic), coatings for greenhouses, aesthetic coatings for solar thermal systems.
- *Coatings for windmills:* Impingement and erosion resistant coatings are necessary to supply market demand for increasingly larger wind turbine blades. On top of that reduced materials use and recycling are of importance for the a large area applications
- *Coatings for aerospace:* anti-icing, anti-drag (micro-aerodynamics)
- Membranes for use in CCU and CCS processes. High performance coatings and membranes for energy transition. e.g. membranes for batteries

D - Coatings, thin films and membranes that contribute to a circular economy

On a planet with limited resources we have to transform linear into circular material flows. Examples of coatings, thin films and membranes that contribute to this objective are:

- Coatings and thin films that contribute to circular packaging, incl. concepts that enable the recycling of current packaging materials and novel design-for-recycling packaging concepts.
- Reversible adhesives that enable removal of materials for recycling/re-use.
- Coatings, thin films and membranes that contribute to a prolonged service lifetime of functional products.
- Membranes that are tailored for recycling processes.
- Membranes for CCU processes.
- Retrofit coatings and thin films developed to restore functionality of existing systems and as such prolong their lifetime.

ChemistryNL

Summary

Topic	Short term (-2025)	Medium term (2025-2035)	Long term (2035-2050)
Traditional coatings, packaging films and membranes	• Development of large scale high precision deposition processes for sub-micron thick functional coatings. • Growth of start-up companies in (multi-)functional coatings and films. • Advanced anti-corrosion coatings to ensure reliability and long-term performance of metallic substrates developed. • Advanced barrier coatings for membranes and packaging films developed. • Non-toxic and durable marine anti-fouling coatings developed.	• Implementation of large scale high precision deposition processes for sub-micron thick functional coatings. • Advanced anti-corrosion coatings commercially produced. • Advanced barrier coatings for membranes and packaging films commercially produced. • Non-toxic and durable marine anti-fouling coatings commercially produced.	
Active, adaptive and instructive systems	• From passive biomedical functionalities to bio-instructive coatings. • Sensoring and signaling coatings developed, e.g. for food packaging materials. • Concepts for active ion transport incorporated in water-permeable membranes developed for low energy desalination. • Concepts for active scavenging or (chemo)absorption of unwanted species developed.	• First responsive/active coatings industrially produced. • First sensoring and signaling coatings commercially applied. • Pilots with membranes for low-energy desalination established. • Pilots with coatings, thin films and membranes for active scavenging or (chemo)absorption of unwanted species.	• Responsive, active and interactive coatings, thin films and membranes industrially produced. • Bio-instructive coatings industrially produced. • Low energy desalination commercially applied.
Coatings, thin films and membranes tailored for energy efficiency, harvesting and storage	• Coatings, thin films and membranes that contribute to the energy transition, focusing on energy efficiency, energy harvesting and energy storage. • Coatings and films for photovoltaics, e.g. for increasing efficiency or prolonged lifetime. First systems commercially produced. • Coatings and films for lighting devices, e.g. for more efficient light extraction or	• Solar control coatings for the built environment: first dynamic systems for intermediate climates commercially applied. • First membranes for use in sustainable chemical processes industrially produced. • First membranes that contribute to the energy transition industrially produced.	• New breakthrough energy harvesting/storage concepts developed to prototypes.

	prolonged lifetime. First systems commercially produced. • Solar control coatings for the built environment: first dynamic systems for intermediate climates produced on lab/small pilot scale. • Concepts for circular impingement and erosion resistant coatings for windmills established. • Concepts for anti-drag and anti-icing coatings for aerospace to reduce fuel consumption developed. • Membranes that contribute to the energy transition. • Membranes for use in sustainable chemical processes such as electrochemical conversions, photochemical conversions, CCU processes.	• First pilots with innovative anti-drag and anti-icing aerospace coatings established.	
Coatings, thin films and membranes that contribute to a circular economy	• Membranes for use in recycling processes developed. • Coatings and thin films that contribute to circular packaging, incl. concepts that enable the recycling of current packaging materials and novel design-for-recycling packaging concepts, developed. • Reversible adhesives that enable removal of materials for recycling/re-use developed. • Coatings, thin films and membranes that contribute to a prolonged service lifetime of functional products developed. • Retrofit coatings and thin films developed to restore functionality of existing systems and as such prolong their lifetime.	• Membranes for use in recycling processes demonstrated in pilots. • First coatings and thin films that contribute to circular packaging commercially applied. • First reversible adhesives that enable removal of materials for recycling/re-use commercially applied. • Coatings, thin films and membranes that contribute to a prolonged service lifetime of functional products commercially applied. • First retrofit coatings/films in pilots.	• Membranes for use in recycling processes commercially applied. • Novel design-for-recycling packaging concepts commercially applied. • Coatings, thin films and membranes that contribute to a prolonged service lifetime of functional products commercially applied.

2.3 Materials for sustainability

Introduction

Materials for sustainability / sustainable materials encompass a wide spectrum of materials and includes materials that are produced in a more sustainable way, make a process/chain more sustainable and/or are used for sustainable energy production or storage" - we include materials based either on polymeric materials, or on inorganic/mineral based materials or hybrid materials.

These materials will have in common: less non-renewable energy use (NREU) and less green-house gas (GHG) emission during the synthesis, construction, processing, packaging, transportation usage, recycling and re-use of these materials. Specific subsets of such materials will even have a positive impact on NREU production e.g. solar cells.

Furthermore, the demand for raw materials increases significantly, such as for oil, rare metals etc. Whereas oil is essential for energy, chemicals and high-performance materials (plastics, fibers, etc.), minerals and metals are crucial in numerous products (electronics, catalysts, solar cells, wind turbines, fertilizers, etc.). A list of 20 critical raw materials was identified by the EU related to supply risks based and economic importance. Clearly, solutions are needed to overcome this upcoming scarcity.

Tasks

Description of the task and the relevance for society, industry and science.

Sustainability is important to accommodate the growth of the world population and its future demand of resources for water, food, energy at higher average life standard. This requires a significant change of today's practice. Changes include the minimization of the manufacturing footprint of the material, but also the sustainable gains of its use during the life cycle and clever re-use of the material or its components. Resources for energy (fossil origin) and raw materials (rare elements) are depleting and this requires a transition to sustainable energy production and reduction, replacement or recycling of rare elements and the further development of renewable or circular materials. The transition to a sustainable society will have a tremendous impact and takes place in stages. Initial efforts are aimed at reducing the footprint by making existing technologies more efficient. Via temporary solutions in intermediate stages, the final goal is a (circular) society based on truly sustainable resources for energy and materials. In this transition to a sustainable society, advanced materials will play a crucial role: a sustainable society cannot be realized without the corresponding materials that enable it.

Solution for this task described SMART (present-2050)

2020-2025 Materials for sustainability / sustainable materials are an emerging field for NL, and also worldwide and will have a tremendous (economic) impact. Our country is too small to leave a large footprint on the planet, but it can contribute to a circular economy of the coming decades, based on two competitive advantages: 1) the excellent knowledge infrastructure for generating (and selling) new technologies, and 2) the high population density and existing organization degree of our society in terms of recycling and energy distribution, enabling for example complicated recovery / separation streams for reuse of materials. We need to try and predict and design the circular material streams, stimulate IP and start-ups and test these hypotheses in small-scale demonstration projects (examples are technologies and materials for additive manufacturing developed in recent years).

2025-2035 In the next decade, regulations (national, EU and global) should be matched with the level of demonstrated circular material use and improved sustainable and clean energy concepts. Supported by this, the scale-up of the envisioned material streams should be implemented. New technologies for material replacement, reduction, reclaim and reuse will lead to large scale industrial activity. Sustainable energy production and storage systems developed in NL, IP protected and sold to areas with larger footprints. This will be supported by the growing image of NL as "designer material" technology provider (2.1.1).

2035-2050 Two decades from now, NL will have settled its name as technology provider for circular use of high value (functional) materials, and sustainable energy materials, based on its knowledge infrastructure as well as its logistic opportunities and its demonstration infrastructure for new technologies in complicated societal environments.

What existing competences, technologies, knowledge contribute to this task?
The existing competences in material (polymer, ceramic) synthesis and manufacturing can greatly contribute to the design and making of new materials / polymers to play their role in sustainability. The chemistry, as such, of these materials does probably not need to be altered completely, just adapted, improved, with enhanced control. For example, in the field of polymers using the existing principles of polycondensation or polyaddition (using renewable or circular building blocks) new polymers can be designed with more advanced functionalities than the present ones. This leaves every opportunity to use NL's leading position in this knowledge field to contribute. NL also has a strong position in research on materials for sustainable energy production, linked to nanomaterials research for harvesting solar energy (PV and more recently solar fuels). The area of clean energy and resource efficient production and reuse processes spans a wide range of chemistry and materials science where in many areas NL has relevant expertise due to the innovative role of the NL chemical industry.

What additional competences, technologies, knowledge do we need?
Raw materials: a closer backward integrating connection needs to be made with the "Making Molecules" roadmap. Also, the design principles ("assemble to disassemble") need to be rethought to enable circular material use and re-use. Research on energy storage (batteries) has declined in NL in the past decades, but offers opportunities for economic activity as the car manufacturing in EU is still strong and NL plays a key role in the supply of materials to this industry. Also, in the field of renewable or circular materials, many efforts are underway. This field, however, needs further time to implementation as cost-effective routes to existing products have to compete with optimized fossil-based assets. The focus should therefore be on truly new materials of biomass / renewable / circular origin. Molecular modelling and coarse grained modelling are expected to contribute to the understanding of the translation of novel building blocks into new materials.

Designing materials with the right functionality

A – Polymeric materials

There are several options to reduce the environmental impacts related to polymer production and use, many of which are also relevant for other bulk materials. Declining reserves of fossil feedstock and the need to mitigate CO_2 emissions enforces an increased use of biomass, other renewable (for instance carbon dioxide offers an accessible, cheap and renewable carbon feedstock for monomer production) or circular resources. In the production of polymeric materials. On the mid to longer term the importance of producing and using renewable and/or circular materials will be of imminent importance. Such materials will be based upon modified natural biopolymers (e.g. starch cellulose, proteins), but increasingly also as a result of polymerizing renewable and/or circular monomers into thermoplastic and thermosetting polymers. Bio-based polymers produced by polymerizing monomers are anticipated to grow even more in importance than the use of modified naturally occurring polymers. Initially polymers based on renewable and/or circular building blocks will have physical properties very much alike todays' petrochemically based polymers. The polymers can be structurally identical to fossil-based polymers (also known as "drop ins" e.g. bio-based polyethylene) as well as based upon unique monomers (e.g. polylactic acid).
Once having an established market share of at least 10% (envisaged for 2030), it will become increasingly important also to derive renewable and/or circular materials with novel or added properties such as improved gas barrier- fire retardancy, antimicrobial, self-cleaning and self-healing or self-assembling properties. In addition the additives used in plastic materials should be reduced to the absolute minimum to facilitate recycling processes and is still strictly required also be based on renewable and/or circular building blocks. A huge challenge is furthermore to develop "triggered degradation concepts" enabling the development of materials with a long life span but which nonetheless can be degraded under appropriate end-of-life conditions or if unintentionally released into the environment (which should of course be avoided strictly)..
In addition, improved waste management by (mechanical and chemical) recycling of materials, re-use and recovery of product components and / or compounds will become more important in the near future. Recycling of petrochemical based polymers is currently dominated by the recycling of PET. Recycling of other polymers like polyolefines should increase in importance and will require the development of novel processing and /or additive technology to be able to maintain material properties and not decrease ("downgrade") material properties while recycling.
In order to enhance the possibilities for recycling, in general materials with less complex formulations (mono-material solutions) will be desired, and the ability to recycle and recover should be regarded as one of the most important

performance characteristics of a material. For materials that are supposed to be used (virtually) as new again ("upcycling"), it is important that they can be separated, not just physically, but also chemically. This still requires a lot of basic research.
"Back to monomer recycling" of polymers will increase in importance, since recycling and use of polymers will inevitably result in material deterioration; Recycling of thermoset materials is a challenge for which dedicated technology should be developed. A promising alternative route is "design for recycling" – during the design of the material future reuse is already anticipated.

Challenges:
(a) With regard to naturally occurring biopolymers such as polysaccharides (starches and cellulose etc.), there is a need for better understanding of their physical properties in relation to their detailed structure, a need for site specific (bio)catalytic modifications strategies and a need for chemistries that allow the product to be modified while avoiding highly polar, potential hazardous solvents (e.g. NMP, DMAA). With regard to lignin as another natural occurring irregular polymer there is a higher need to develop chemo- or biocatalytic strategies to obtain well defined products at higher value. Improved biotechnological modification strategies should enable us to use these products in a broader range of applications, including e.g. water based paints, coatings, adhesives, dishwashing formulations, cosmetics etc., but also in more durable products like agrofibre reinforced materials or bio-based plastics. This will also lead to the envisioned novel or added properties.
(b) New routes to turn CO_2 into monomers and polymers will become a key driver to accelerate and facilitate the transition from existing fossil-based to future generations of renewable or circular materials. Catalysis is the key enabling technology / challenge in this respect, providing new opportunities to turn this carbon feedstock into valuable materials.
(c) With regard to identical "drop-in" chemicals (and the polymeric materials based upon them) the challenge is to develop technology to optimize biorefinery systems for generating the feedstock and optimizing biotechnological or chemo-catalytic modification methods to get to efficient ways of synthesizing the identical, drop–in chemicals. For unique molecules and materials, development of efficient synthesis routes as well as the synthesis and exploration of new unique materials based upon these monomers should go hand-in-hand.
(d) an additional challenge for renewable or circular polymers results from polymer additives (including processing aids, lubricants, heat stabilizers, antioxidants, pigments etc.) and auxiliary agents (e.g. catalyst, solvents) with reduced Health, Safety, Environment (HSE) issues. Materials for sustainability will also require polymer additives with substantially reduced HSE issues compared to many of the current ones (e.g. lead based heat stabilizers, brominated flame retardants etc.). Furthermore, polar solvent that are very important to the current and future industry like NMP, DMSO and DMAA should be replaced. It is of absolute importance to develop new classes of additives and solvents, designed and engineered for optimal functioning in new renewable or circular polymers.
(e) End-of-life solutions such as recycling and chemical/physical recovery are in their infancy in the Dutch academic and industrial landscape. A strong focus should be put on this topic to not miss this important opportunity to close the loop in the field of materials for sustainability. Life cycle analysis (LCA) should be included as much as possible when assessing materials production, use and end-of-life.

B - Sustainable synthesis and production - Increased energy efficiency and material efficiency (yields) in all processes in the value chain leading to more sustainable products
Over the years, chemical processes have continually improved in terms of their greater utilization of (secondary) raw materials, improved safety and increased productivity whilst minimizing waste and energy use. Yet, chemical industry is still facing the need to restructure and modernize by continuing to reduce energy as well as resources consumption (i.e. both raw materials and water) besides reducing waste as amounts and emissions at the same time.
Challenges:
To achieve near 100% selectivity in multi-step and complex syntheses. Exploration of new reaction pathways and conditions, reduction of the number of reaction steps, introduction of intensified separation technologies and intensification in the energy input; design of integrated processes, adapted materials (i.e. membranes for hybrid separations), solvents (i.e. ionic liquids for extraction) as well as equipment.

C - Sustainable materials for energy
As high-density energy sources like fossil fuels will take more energy to access in the future, advanced materials will be used to fulfill our energy demand. Cost-effective and energy efficient options for capturing, converting and storing

naturally available energy (solar, mechanical, thermal etc.) are highly sought after. New materials and chemical synthesis routes will provide these novel materials in the future. Photovoltaic materials like perovskites can convert light into electricity and other inorganic materials can be used to store energy in batteries.

Solar cells are already the most cost-effective option for sustainable electricity generation. However, the production of solar electricity needs to grow by about two orders of magnitude within two decades. Such enormous growth needs higher efficiency to reduce the impact that this form of electricity generation has on the environment, and ways to fabricate these solar cells at much faster rate. Foil-based solar cells and tandem geometries are ways to produce solar cells at an unprecedented speed and efficiency, and with much lower resource intensity (earth-abundant materials, low energy consumption during fabrication, fast roll-out). These solar cells require innovation in materials, interfaces and device design.

The use of materials for energy storage is expected to develop impressively in the coming decades. The need for storage of electrical energy, generated by a plethora of technologies – on large scale (the “grid”) as well as small local scale, will steeply increase. On the one hand this energy can be stored in reversible chemistry, such as in well-known in batteries (Li cells) but also in for example hydrogen cells. Recent battery developments have shown considerable progress in terms of energy density (J/Kg) but still faces challenges and limitations in terms of power density (W/Kg), while the different needs for energy storage will be requesting breakthroughs at both fronts (transport, portable devices, local solar facilities). Supercapacitators hold promise for higher power densities, but are still in their (technology) infancy. Polymer supercapacitators are in need for reliable multi-lamination technology of thin films (see also 3.2) with step-change increased electrical breakdown resistance.

Challenges:

Materials and processes are needed that can meet the energy demand. Materials composed of non-critical elements will ensure availability and reduce the cost for market introduction. Durable materials are needed that have a long lifetime or can be easily recycled. For phase-changing materials, mechanical stability is an additional issue that needs to be addressed. Processes are needed that can deliver the volumes associated with the application markets. The energy required for these processes should be kept as low as possible, since this effectively reduces the energy that can be generated with these materials.

Summary

Topic	Short term (-2025)	Medium term (2025-2035)	Long term (2035-2050)
Polymeric materials	• Develop renewable or circular building blocks • Develop sustainable polymeric materials based on “drop in” renewable or circular monomers or novel building blocks • Design of better recovery rates and more efficient mechanical recycling methods • Design of the next generation of technology for effective chemical recycling, including (bio)catalysts	• Further development of technologies for renewable or circular additives like plasticizers, flame retardants and lubricants from TRL5-6 to 9 • Establishing LCA studies for all commercial materials use • Scale up of mechanical & chemical recycling technologies	• Scaling up and usage of renewable or circular materials • Implementation of materials developed in “design for recycling” projects • Circular use of all commodity plastics established
Sustainable synthesis	• Further development of (bio)refinery technologies (especially relevant for chemical conversion roadmap) • Design of the next generation of multifunctional (bio)catalysts by integrating knowledge on hetero-, homo-, single-site and biocatalysts (see catalysis roadmap) • Development of improved (bio)catalyst technologies enabling improved control over molecular architecture of polymers and polymerizations at lower temperatures and lower energy input	• Intensified reaction and process design (including smart design of the synthetic route, micro process technologies, catalytic reactions, fluid dynamics, separation technology, particle technology, advanced process control, integration and intensification of processes combined with new catalyst concepts and increasingly sophisticated computer modelling of chemical interactions and plant simulation	• Increase energy- and resource-efficiency and reduce waste as well as emissions generation in all processes in the production chain

Sustainable materials for energy	• Understanding and modelling of the phase stability of novel materials • Understanding and modelling of the properties of novel materials • Optimizing materials for efficiency and stability (e.g. thin film perovskite solar cells with high radiative efficiency) • Stable, selective and conductive interface materials that can be processed in a roll-to-roll fashion • Develop academic and industrial research lines centered on energy storage and electrochemistry	• Prediction of phase stability of novel materials • Prediction of properties of novel materials • Understanding and modelling of mesoscopic properties • Light-management strategies for tandem solar cells • Development of fast, scalable fabrication techniques for foil-based solar cells	• Ab initio prediction of materials based on material properties • Implement designed energy production and storage solutions in industrial commercial context • Integration of, and interaction with the environment and ecosystem in solar parks of the km^2 scale

ChemistryNL

Roadmap
Chemistry of Life

ROADMAP CHEMISTRY OF LIFE

1. Introduction

Understanding of Life on a molecular level (Chemistry of Life) provides a key that unlocks unlimited opportunities for breakthrough innovations, needed to address our global challenges for people today, and generations to come. The unifying aim in Chemistry of Life is therefore to bring about the chemical means and molecular understanding leading to an improved, more precise, personalized and effective healthcare as well as more sustainable and healthy food for the benefit of mankind.

Life entails a complex collection of molecules that enable, regulate, improve or threaten life. During the past century, scientific breakthroughs in (bio)chemistry led to the identification of molecules which are building blocks of life. We increasingly understand their functions, how they interact with small molecules and how they contribute to life. The fundamental understanding of the building blocks of life is applied in industries to develop products, improving life for individuals and society as a whole. While progress is enormous, leading to novel and targeted medicine and securing our food supply for a growing population, we still face major gaps in our understanding of life on a molecular level. At the same time, we are confronted with great challenges in healthcare as well as a sustainable healthy food supply.

What are the next scientific breakthroughs in Chemistry of Life? How can the Netherlands contribute to these by using and further developing our excellent knowledge infrastructure and network of world class universities, knowledge institutes and the private sector? How can we capture innovations and economic growth in The Netherlands based on these breakthroughs (e.g. through our world-class food production systems and by expanding current vibrant biotech start-ups and establish novel ventures)?

The answers will come from **collaborations**. Collaborations across disciplines, across industries (value chains), and across the world. The Chemistry of Life roadmap therefore has a focus on chemistry and molecular insights that will be embedded in all sectors that contribute to the scientific and economic breakthroughs the top sector Chemistry wishes to enable. These connections are further specified in section 4.

A three-pillar (task) roadmap has been developed to address the scientific challenges and economic opportunities in healthcare (task 1) and food/nutrition (task 2) and the link between them, connecting health and food/nutrition (task 3).

The **first pillar** (task 1) focuses on ‘Molecular entities, devices and approaches for understanding, monitoring and improving **precision 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 (therapeutic) approaches that prevent diseases, or re-program and revert cells to a normal healthy state or trigger cell death (apoptosis) to eliminate defective cells. Genomics, transcriptomics, proteomics, metabolomics data (omics) obtained using advanced (clinical) analyses of patient material constitute a treasure trove to understand and redirect molecular pathways. Fundamental disciplines including molecular biology, biochemistry and medicinal chemistry together define the relevant interactions and events disturbed in disease and targeted in therapy. Emerging infectious diseases and antibiotic resistance are urgent health threats that can only be addressed with new chemical insights and knowledge and its applications. The identified health(care) related chemical processes can then be targeted by existing or newly developed drugs with more precise and efficient effect. Thus 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.

The **second pillar** (task 2) focuses on ‘Molecular entities, technologies and approaches for understanding, monitoring and improving food to ensure a sustainable supply of safe and nutritious, delicious food and feed to optimize health and wellbeing’. The Netherlands is leading in the application of technological solutions to food production and food security with for example Unilever, DSM and Danone Nutricia as key industrial parties located in the Netherlands. Chemistry is an essential element in food innovation. Chemistry will also enable the food sector to get to the next level in answering fundamental scientific questions to provide breakthrough innovations that address societal needs related to food quality and security throughout the whole lifespan. Sustainable food production and an increased contribution of renewable (plant-based) food to the human 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. In addition, it is crucial to understand which molecules are present, the exact location and understand how these molecules mutually interact and build the supramolecular systems in foods responsible for flavour and taste as well as nutritional features and bioavailability of food nutrients.

The **third pillar** (task 3) focuses on **enabling technologies** and approaches for fundamental understanding, monitoring and improving molecular entities in the Chemistry of Life. This pillar creates 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 bio-inspired materials, circular economy and sustainable energy. Thus 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.

	Short term **Now-2022**	**Mid term** **Now-2030**	**Long term** **2030-2040**	**Programme Line ambition**
Molecular entities, devices and approaches for understanding, monitoring and improving precision healthcare	- Personalized omics analysis - Drug development for orphan diseases - Understanding material properties contributing to improved compatibility with human bodies and cells.	- Target identification for (multifactorial) diseases - Multidisciplinary multi-centre of Drug Discovery (e.g. Future Medicine Initiative) which enforces the cluster Chemical technologies in the KIA Key Technologies - Structural information on the interaction of NCEs and bio-conjugates with target proteins - Explore new functionalities of Materials in human bodies (e.g. stability, release, mechanical strength, lubrication, antimicrobial, molecular detection and reporting) which enforces the cluster Advanced Materials in the KIA Key Technologies	- Development of novel clinically affordable disease- oriented workflows and devices directly enforcing Mission II Access to Healthcare (KIA Health & Care) - Development of New Chemical Entities (NCEs), biopharmaceuticals and bio- conjugates for use in diagnostics, in vivo imaging, and clinical applications - Piloting and commercialization of new materials and devices	*Improved and more affordable precision healthcare*
Molecular entities, technologies and approaches for understanding, monitoring and improving food to ensure a sustainable supply of safe and nutritious, delicious food and feed to optimize health(care) and wellbeing	- Molecular understanding of factors impacting texture/taste - Validated biomarkers of nutritional status in order to progress from descriptive models to predictive models - Development of products that improve nutritional status and optimization of guidelines and dietary	- Novel enzymes/microbes that tailor texture/taste both *in-situ* and *ex-situ* - Quantitative and mechanistic models of in vitro and in vivo digestion of foods based on biochemical properties of food constituents - Novel biochemical processes for obtaining ingredients with reduced	- New, biochemically derived health promoting substances, including enzymes and micro-organisms with a link to life science technologies: ST7-4 Gene Editing / Precise Genetic Engineering - Correlation of in vitro and in vivo digestion models: what happens during digestion in humans	*Improved and more sustainable food*

	recommendations - Identification of new, optimal chemical processing of new, sustainable sources for protein supply which enforces the KIA Circular Economy; MMIP2AQ3 - Adapt feeds to reduce nitrogen, phosphate and/or sulphur emission which enforces the KIA Circular Economy; MMIP2AQ11.	environmental footprint - Molecular localization methods including spatially and time resolved analysis tools for food ingredients and finished products	and full functionality of whole GI tract including taste and texture - Novel ingredients to replace current, undesired food additives that are used to reduce spoilage supporting the missions formulated in the KIA LWV and the KIA CE.	
Enabling technologies and approaches for fundamental understanding, monitoring and improving molecular entities in the Chemistry of Life	- Insight into the impact of the heterogeneity of proteins and protein complexes on cellular networks - Building Blocks of Life, 16 projects that are currently running, supported by TKI Chemistry together with other topsectors which support the missions formulated in the KIA LWV and the KIA Health & Care and enforces the cluster Life Science Technologies in the KIA Key Technologies - Novel biocatalytic enzymes carrying out unique chemistries	- Influence of heterogeneity in the dynamics of bio molecular networks and on the robustness of systems - Minimal cells that conduct specific biochemical reactions and biotransformations in a robust manner and that can be used in industrial applications related to bioenergy, biomaterials, chemical production - Markers for food quality and spoilage and food borne pathogens supporting the missions formulated in the KIA LWV and the KIA CE.	- Utilize the knowledge on network dynamics and cellular heterogeneity to tackle challenges in energy, food and health(care). - Synthetic cell-like entities (eukaryotic and prokaryotic) that in a controlled manner carry out complex coupled processes including basic biochemical reactions that can replicate - “Organ-on-a-Chip” modules that can be used as a disease specific screening	*Accurate cell systems for medical, food and energy applications*

Table 1

ChemistryNL

ChemistryNL Roadmap	Energy Transition and Sustainability			Agriculture, water and food	Health and Healthcare	Security	Key Technologies	Societal earning capacity
	Climate and Energy (IKIA) *in particular Mission C "Industry"*	Circular Economy	Future Mobilitysystems	7 missions	4 missions	8 missions	Key technnology (ST) clusters: ChemTech, AdvMat, DigTech, EngFabTech, LifesciTech, NanoTech, PhotoTech, QanTech	3 tracks
Chemistry of Life							LifeSciTech, ChemTech	
Molecular entities, devices and approaches for precision healthcare		(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.			Wearable diagnostic devices eliminate the need for visiting the hospital, are instrumental to avoid clearly dangerous environmental chemical entities or enable to remove these from environment (smart filters/absorbers) and prevent disease and directly enforces Mission II, access to healthcare of the KIA Health & Care		Creation of new chemical, molecular, biological and cellular entities to interact with and predictably modify chemical properties of biomolecules for treatment and the exploration of new functionalities of Materials in human bodies enforces the cluster Advanced Materials in the KIA Key Technologies ; New, biochemically derived health promoting substances, including enzymes and micro- organisms link to life science technologies: ST7-4 Gene Editing / Precise Genetic Engineering	
technologies and approaches for understanding, monitoring and improving food to ensure a sustainable supply of safe and nutritious delicious food and		Biochemical tailoring of food, Sustainable production, longer shelf life of food products and new sources of e.g. proteins and the development of novel ingredients to replace current, undesired food additives that are used to reduce spoilage supporting the missions formulated in Mission CE (MMIP2AQ3) and also the adaptation of feeds to reduce nitrogen, phosphate and/or		Biochemical tailoring of food, Sustainable production, longer shelf life of food products and new sources of e.g. proteins and the development of novel ingredients to replace current, undesired food additives that are used to reduce spoilage supporting the missions formulated in the KIA LWV; Mission B & D			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 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 and enforces the cluster Life Science Technologies in the KIA Key Technologies.	
Enabling technologies and approaches for fundamental understanding, monitoring and improving molecular entities in the Chemistry of Life		Designer minimal cells for application and production in bioenergy, biomaterial and (bio-)chemical production and Markers for food quality and spoilage and food borne pathogens support mission CE		Designer minimal cells for application and production in bioenergy, biomaterial and (bio-)chemical production and Markers for food quality and spoilage and food borne pathogens and Building Blocks of Life projects support the missions formulated in the KIA LWV; Mission B &D	Building Blocks of Life support the missions formulated in the KIA Health and Healthcare; Mission I, II and III; The chemical knowledge generated for diagnostics and the information on the chemical status in a body contributes to the KIA Health & Care, mission I (lifestyle and environment) and mission III (chronic diseases). Cell like entities as smart diagnostic and therapeutic agents contribute to the improvement of health and healthcare, the overall aim of the KIA Health & Care.		Building Blocks of Life support and make use of Key Technologies; Designer minimal cells for application and production in bioenergy, biomaterial and (bio-)chemical production support the cluster Advanced Materials in the KIA Key Technologies; Tailor made platforms for high throughput drug screening.	

2. Collection of tasks

A unifying aim in the Chemistry of Life theme is to bring about the chemical means that facilitate improved and more affordable precision healthcare and more sustainable and healthy food, both benefitting the future of mankind.

2.1. **Task 1**: Molecular entities, devices and approaches for understanding, monitoring and improving precision healthcare are relevant for e.g. cancer diagnosis, prognosis and treatment. Insight into specific molecular defects and targeting of these targeted strategies appear effective, but not all molecular defects developed as treatment targets can overcome treatment failure and recurrence. More detailed understanding of the complex responses based on understanding of the integrated chemical network of cells is key. This is equally relevant for other chronic diseases of tissue degeneration (neurodegeneration, circulatory system, joints) where chemical clues can be used as early warning and chemical intervention needs to be designed to reach the specific sites involved and have the desired regenerative effect. This task directly supports mission III of the KIA Health & Care (chronic diseases).

2.1.1 Development of analytical and biophysical devices (e.g. chemical read out on biopsy samples, molecular imaging for non-invasive imaging applications, computational tools for -omics analysis of complex traits) which enforces Mission II Access to Healthcare (KIA Health & Care)

2.1.2 Creation of new chemical, molecular, biological and cellular entities to interact with and predictably modify chemical properties of biomolecules for treatment (e.g. eliminate cancer cells, restore neuronal function, repair degenerated joint tissue, kill microbes and virus infected cells, or prevent infection, stimulate immune responsiveness specifically to diseased cells, address orphan diseases). Explore new functionalities of materials in human bodies (e.g. stability, release, mechanical strength, lubrication, antimicrobial effect, molecular detection and reporting) which enforces the cluster Advanced Materials in the KIA Key Technologies

2.1.3 Biomedical materials for improved functionalities (with applications in transplantation, joint repair, to increase the longevity and function of *ex vivo* organoids or biopsies, enabling study and diagnosis, scaffold cells for tissue repair and delivery of therapeutic chemicals in a localized and controlled way) which enforces the cluster Advanced Materials in the KIA Key Technologies

2.1.4 Lifestyle & environment (wearable diagnostic devices eliminate the need to visit the hospital, are instrumental to avoid clearly dangerous environmental chemical entities or to remove these from environment (smart filters/absorbers) and prevent disease) and directly enforces Mission II of access to Healthcare (KIA Health & Care)

2.1.5 Sustainable production (devices and entities that biodegrade, are smaller and do not need to be disposed of and stimulate re-use in complex synthesis and production). This can be linked with the cluster Chemical technologies in the KIA Key Technologies.

2.2. **Task 2**: ‘Molecular entities, technologies and approaches for understanding, monitoring and improving food to ensure a sustainable supply of safe and nutritious, delicious food and feed to optimize health and wellbeing and to prevent noncommunicable (like cardiovascular disease, diabetes and cancers) and neurodegenerative diseases (like dementia). This task directly supports the central mission of the KIA Health & Care and specific missions III (chronic diseases) and IV (dementia).

2.2.1. Biochemical tailoring of food. 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. Altering the food chemical composition can also aid to make the food last longer and better maintain nutrients in storage and transport. Thus supporting the missions formulated in the KIA LWV and the KIA CE

2.2.2. Understanding food digestion and metabolism to increase nutritional availability and health. Correlate in vitro and in vivo digestion models to explain what happens during digestion in humans and full functionality of the whole GI tract including taste and texture

2.2.3. Sustainable production and consumption. Feeding the ever-increasing world population in a sustainable manner is becoming a true challenge which is also addressed in the KIA LWV and the KIA Circular Economy. Through this Chemistry of Life roadmap, new sources of e.g. proteins are currently being implemented. Consumer acceptance is modest due to flavour and taste defects caused by the presence of off-flavours generated in the growing of plants or in later food manufacturing and storage. Blocking (enzymatic) formation routes and other mitigation strategies require a detailed molecular understanding of (plant) cellular mechanisms.

2.3. **Task 3**: Enabling technologies and approaches for fundamental understanding, monitoring and improving molecular entities in the Chemistry of Life
2.3.1 Understanding of cellular processes from molecule to organism
2.3.2 Engineering of molecules and cells
2.3.3 Technologies to measure and track food deterioration and food borne pathogens

3.1 Task 1: Molecular entities, devices and approaches for understanding, monitoring and improving precision healthcare

In the Chemistry of Life Program first of all, **analytical and biophysical tools and methods** need to be further developed that assist us to monitor the molecular entities, not only in our body, but also in animals, plants, fungi and other organisms. In the future human, animals and plant, healthcare will only be more intertwined. For future healthcare such approaches will allow us to develop new diagnostics for early discovery and enable a more personalized and precise health care monitoring and disease prevention. This will enable one to monitor the status of healthy individuals, and of patients with chronic diseases and detect disease in more early stages. Impact of lifestyle, and environment on health can also be monitored by these means. Additionally, they will help to balance safety and efficacy in the nutrition chain.

Importantly, new molecular and cellular entities will be synthesized and/or designed, ranging from highly selective inhibitors to adapted cellular therapies (such as stem cells and gene therapies and tailor- made vaccines). This Task is related to the central mission of the KIA Health & Care and specific missions II (Access to healthcare) and III (chronic diseases).

3.1.1 Development of analytical, biophysical 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 ineffective for some patients and drug resistance may occur. Quantitative patient-derived **omics analysis** and model-based predictions (using big data and artificial intelligence) constitute a treasure trove to understand which molecular pathways are affected and may be targeted by (existing) drugs, thus offering an avenue towards precision medicine.

To achieve this:

We need to explore and develop analytical and biophysical strategies and devices, cellular model systems 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, cluster Life science technologies Q2 (develop reliable implants that monitor and/or treat medical conditions) and Q3 (developing medical devices that monitor body parameters and medical conditions invisible on the skin or easily accessible at home or in primary care for preventive healthcare or the monitoring of chronic diseases) and chemical technologies ST1-2 Analytic Technologies Q2 (develop micro-analytical systems to measure cellular structures and body fluids in real-time with techniques for multiscale analysis of the local molecular processes and the related medical conditions).

Specific steps required present-2040:

I. Development of diagnostic workflow/devices:

- Establish large-scale multi-centre infrastructures for the quantitative analysis of all bio-molecular entities such as the Future Medicine Initiative (genomics, proteomics, metabolomics, structural biology, bio-imaging, chemical biology 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

II. Obtain novel insights into molecular mechanisms of disease

- Develop novel synthetic and cellular platforms/model systems (e.g. pluripotent stem cells (iPSCs) derived cells/organoids; 3D cellular co-cultures; multiplex high content imaging) and analytical tools 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
- 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 (multifactorial) intervention and targeting.

<u>Milestones:</u>

- Personalized omics analysis, relevant robust markers of disease process identified and validated
- Establishment personalized (iPSCs-based) (2/3D) multi-cellular model systems (cells/organoids)
- Target identification for (multifactorial) diseases
    - Enabled 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 care

<u>Expected results present- 2040:</u>

Scientific/technological goal: Target-based therapy established on disease network analysis.

Industrial end goal: Translation of diagnostic tools and analysis to commercialization.

Societal goal: Cohort of patients performing disease related self-diagnosis or self-monitoring thus contributing to Mission II (Access to Healthcare) of the KIA Health & Care

3.1.2 Creation of new chemical, molecular and cellular entities

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 or antibody-based approaches 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 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-, 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:

I. Assay development for selection of bioactive (bio)molecular entities:

- Development of novel miniaturized assay formats for High Througput 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.

II. Design and synthesis of new (bio)molecular entities which enforces the cluster Chemical technologies in the KIA Key Technologies :

- Synthesis and biochemical programs aimed at the development of bioactive molecules that can serve as therapeutic agents. 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.
- Structure-based drug design (SBDD)
  - Obtain structural information of target protein to develop 3D molecular models of targets.
  - Binding mode prediction and (virtual) screening for selection of candidate molecules.
  - Parallel high throughput crystallography and structure determination.
  - Design and optimization of molecular entities.

Milestones:

- Development of NCEs, biologicals and bio-conjugates for use in 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

○ Multidisciplinary multi-centre of Drug Discovery:
  - Establishment of a centralized infrastructure to prepare, store, analyse, model and test Dutch collections of small molecules and bioactive compounds for HTS and high content screening purposes.
    - Compound logistics
    - IP issues (or open source innovation plan)
    - Outreach to partners with relevant targets
  - Further development of drug candidates and biologicals into new affordable medicines and affordable entities for diagnosis and therapy.
    - Coordinated small molecule synthesis, medicinal chemistry, chemical biology based approaches and central screening and characterisation both in vitro and cell- based and high content.
    - Public-private partnerships for further development of NCEs.

Expected result present- 2040:

Scientific/technological goal: development (bio)molecular entities for diagnostic and therapeutic applications. This will require a Dutch multidisciplinary centre for Drug Discovery providing HTS services and high content screening.

Industrial end goal: New diagnostic probes, high quality NCEs, biologicals for further development towards marketed drugs that serve unmet medical areas. Establishment of novel ventures.

Societal goal: New diagnostics and new drugs leading to, healthier living, and better health(care), and better understanding and control of disease by affordable small molecules or biologicals thus contributing to the KIA Health & Care.

3.1.3 **Biomedical Materials for improved functionalities,** which enforces the cluster Advanced Materials in the KIA Key Technologies

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, 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, muscoskeletal, nephrology, drug delivery systems and implants. This is related to the KIA Key technologies, cluster Life science technologies Q2 (develop reliable implants that monitor and/or treat medical conditions) and Q3 (developing medical devices that monitor body parameters and medical conditions invisible on the skin or easily accessible at home or in primary care for preventive healthcare or the monitoring of chronic diseases) and chemical technologies ST1-2 Analytic Technologies Q2 (develop micro-analytical systems to measure cellular structures and body fluids in real-time with techniques for multiscale analysis of the local molecular processes and the related medical conditions).

Specific steps required present-2040:

I. Understanding material properties contributing to improved compatibility in human cells.

II. Explore new functionalities of Materials in human bodies (e.g. stability, release, mechanical strength, lubrication and antimicrobial).

III. Development of new materials and devices.

IV. Piloting and commercialization of new materials and devices.

Milestones:

- New insights in basic principles created
- proof of principles established

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.

Examples of MJPs related to this pillar:

MJP02 Building Blocks of Life Begrip en benutting van cellulaire sytemen

MJP13 Smart personalized food and medicine

MJP16 MedTech

MJP17 Biomedical Engineering for Health

MJP71 Meet- en Detectietechnologie

MJP72 Evidence Based Sensing

MJP86 Bridge – Life Science Technologies

MJP87 Vitality, Lifestyle and Ageing-in-place for people with (early) dementia

Examples of initiatives related to this task:

Gravity Programs such as Institute of Chemical Immunology and Cancer GenomiCs.nl, Roadmap Infrastructure Proteins@Work and uNMR.nl, TI-COAST, Pivot Park Oss, European Innovative Medicines Initiative (IMI), FIGON, Roadmap NL-BioImaging AM, DTL, OneHealth and CeSAM.

3.2 Molecular entities, technologies, devices and approaches for understanding, monitoring and improving food to ensure a sustainable supply of safe and nutritious, delicious food and feed to optimize health and wellbeing

3.2.1 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 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 and support the missions formulated in the KIA LWV and the KIA CE and enforces the cluster Life Science Technologies in the KIA Key Technologies. (Biochemical) Tailoring exploiting 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.

<u>To achieve this:</u>

Biochemical tailoring of food and food ingredients (including live/viable cultures) should include:

a. Understanding the production routes of (off-) flavour and taste compounds in plants and methods to modify these.
b. Enzymatic or microbial production of flavour, texture and health supporting substances.
c. Molecular understanding of the food matrix and ingredient (enzymes, microbes) interaction leading to a desired food performance.
d. <u>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 taste and texture sensing</u>

<u>Specific steps required present-2040:</u>

Short term:

I. Identify relevant flavour forming reactions in foods and fermented foods that can or have to be improved, both in situ in foods and ex-situ productions of flavours
II. Identify specific locations of molecules, quantify intermolecular interactions in foods and understand how molecules build multiscale structural organisations affecting protein binding, the uptake of nutrients and the experience of flavours
III. Identify suitable health promoting substances that are formed by a limited number of enzymatic reactions, using microbes or that are plant derived.
IV. Advancing sensory science (texture, taste/flavour combination).

Long term:

V. Produce and apply enzymes or microbes to improve or stabilize flavour in foods and/or ingredients.
VI. Enhanced production of taste, nutrition and health promoting substances within the food matrix.
VII. Cascading enzyme reactions including activation of desired nutrient formation routes and inactivation of formation routes of off-flavours or natural toxins or anti-nutrients.
VIII. Connecting sensory science (incl. texture/taste combination) with molecular 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/taste.
- Novel enzymes/microbes that tailor texture/taste 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. Thus supporting the missions formulated in the KIA LWV and the KIA CE.

3.2.2 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. More specifically, this includes:

a. Identifying biomarkers of pre- and probiotics
b. Nutritional value: Understanding digestion kinetics (*in vitro* and *in vivo*).
    - Understanding of enzymatic/fermentation kinetics relevant for the food bolus; Enzymology of “Crowded system dynamics”.
    - Understanding molecular interactions during digestion/fermentation processes.
c. Dynamic effects of metabolized food components (host, microbiota and interplay between the two) on tissue and organ functions (e.g. brain, muscle, immune system, gut).
    - Engineering of food to target specific organs or cells.

Specific steps required present-2040:

Short term

I. Establishment of mechanistic molecular descriptors of hydrolysis/fermentation kinetics of food constituents.
II. Establishment of physico-chemical descriptors of hydrolysis/fermentation processes of food constituents in semi-solids systems.

Quantitative correlations between the microbiota composition and the occurrence and/or formation of prebiotics during intestinal fermentation.

Long term

III. 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).

Milestones

- Validated biomarkers of health and disease in order to come from descriptive models to predictive models.
- 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 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 the (bio)chemistry of health and disease. Thus supporting the central mission of the KIA Health & Care.

3.2.3 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. A biochemical approach is key to this development, thereby improving the sustainability of food supply. Knowledge of the chemistry and the molecules involved again is crucial.

This enforces the cluster Chemical technologies in the KIA Key Technologies; Q5 to develop cheap ad efficient electrochemical processes for the conversion of H20, CO2, N2 or biomass to fuels and raw materials for the chemical industry explicitly including the required scaling of these processes to GW level in the design and ST1-1 (Bio) process Technology Q1 Develop sustainable and effective conversion of biomass to raw materials and specialty chemicals through micro-organisms for example for waste water conversion

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:

a. 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.

b. 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 supporting the missions formulated in the KIA LWV and the KIA CE.

Specific steps required present-2040:

Short term

I. Development/adaptation of analytical methods to be used in concentrated and/or crowded systems.

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

Long term

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

<u>Milestones:</u>

- 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.

- Novel ingredients to replace current, undesired food additives that are used to reduce spoilage by natural alternatives.

<u>Expected result present- 2040:</u>

Scientific 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. Thus supporting the missions formulated in the KIA LWV and the KIA CE

Examples of MJPs related to this pillar:

<u>MJP04 High Tech to Feed the World</u>

<u>MJP06 Verbetering van de fotosynthese-efficientie</u>

<u>MJP13 Smart personalized food and medicine</u>

<u>MJP87 Vitality, Lifestyle and Ageing-in-place for people with (early) dementia</u>

Examples of MMIPs related to this pillar:

MMIP2A Q11: stikstof en fosfaat

MMIP2A Q3: eiwittransitie

MMIP2A Q7: voedselverspilling

Examples of initiatives related to this task:

Carbohydrate Competence Center (CCC), multiple programmes within WageningenUR Food and Biobased Research, JPI a Healthy Diet for a Healthy Life, Top Institute Food and Nutrition (TIFN).

3.3. Enabling technologies and approaches for fundamental understanding, monitoring and improving molecular entities in the Chemistry of Life

This links to all Life Science technologies of the KIA Key Technologies and the cluster chemical technologies ST1-1 (Bio)Process Technology Q1: Develop sustainable and effective conversion of biomass to raw materials and specialty chemicals through micro-organisms for example for waste water conversion and to ST1-2 Analytic Technologies Q2: develop micro-analytical systems to measure cellular structures and body fluids in real-time with techniques for multiscale analysis of the local molecular processes and the related medical conditions.

3.3.1 Understanding of cellular 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 fulfil 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:

I. Understanding of complex cellular networks with an emphasis on dynamics.

Use of advanced methods in molecular imaging, ribosomal profiling and mass spectrometry to map cellular networks and their dynamics, and employ molecular biology, optobiology and chemical biology to perturb network processes and identify relevant physiological response.

II. 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.

III. Quantitative description of biochemical processes in individual cells.

- Elucidate the molecular basis of cellular heterogeneity by large scale imaging 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 computational modelling, 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.

Industrial end goal: Application of single cell network theory describing meta-stability 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.

3.3.2 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. We propose 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 and material development; in diagnostics, and to collect information on the chemical status in a body and report back via non-invasive imaging, 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. Especially the diagnostics and the information on the chemical status in a body contributes to the KIA Health & Care, mission I (lifestyle and environment), mission II (access to Healthcare) and mission III (chronic diseases).

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 predicable function. In the top-down approach, existing cells and cellular systems are exploited and modified to re-programme their function for specific tasks. This also involves harnessing cell heterogeneity for complex functions including mimicking organs.

Specific steps required present-2040:

I. 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.

II. 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 industrial applications related to bioenergy, biomaterials, 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

Examples of MJPs related to this pillar:

MJP01 Fenotype-Genotype-Prototype

MJP02 Building Blocks of Life Begrip en benutting van cellulaire sytemen

MJP06 Verbetering van de fotosynthese-efficiëntie

MJP14 Maatschappelijke gewenste en veilige biotech toepassingen door Safe-by-Design

MJP17 Biomedical Engineering for Health

MJP86 Bridge – Life Science Technologies

MJP92 Medische Isotopen

Examples of connections to other platforms:

Gravity Programs such as BaSyc (synthetic cells), Netherlands Organ on a chip initiative, Institute of Chemical Immunology, Cancer GenomiCs.nl, Roadmap Infrastructure Proteins@Work, uNMR.nl, and Nanofront, Kluyver Centre for the genomics of industrial fermentations, BE-Basic (on sustainable biobased processes), Centre of Synthetic Biology at the University of Groningen, BioSolar Cells, Top Institute Food and Nutrition (TIFN), Human disease model on a chip (hDMT), research facility UNLOCK (Unlocking microbial diversity for society) and FOM Institute AMOLF.

Contribution of this Chemistry of Life roadmap to the Mission driven research

- (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.
- Identification of new, optimal chemical processing of new, sustainable sources for protein supply which enforces the KIA Circular Economy; MMIP2AQ3
- Adapt feeds to reduce nitrogen, phosphate and/or sulphur emission which enforces the KIA Circular Economy; MMIP2AQ11.
- Utilize the knowledge on network dynamics and cellular heterogeneity to tackle challenges in energy, food and health(care).
- New, biochemical derived health promoting substances, including enzymes and micro- organisms is linked with life science technologies: ST7-4 Gene Editing / Precise Genetic Engineering Q6
- Wearable diagnostic devices eliminate the need for visiting the hospital, are instrumental to avoid clearly dangerous environmental chemical entities or enable to remove these from environment (smart filters/absorbers) and prevent disease) and directly enforces Mission II, access to healthcare (KIA Health & Care)
- Explore new functionalities of Materials in human bodies (e.g. stability, release, mechanical strength, lubrication, antimicrobial, molecular detection and reporting) which enforces the cluster Advanced Materials in the KIA Key Technologies.
- Creation of new chemical, molecular, biological and cellular entities to interact with and predictably modify chemical properties of biomolecules for treatment (e.g. eliminate cancer cells, restore neuronal function, repair degenerated joint tissue, kill microbes and virus infected cells, or prevent infection, stimulate immune responsiveness specifically to diseased cells, address orphan diseases) Explore new functionalities of Materials in human bodies (e.g. stability, release, mechanical strength, lubrication, antimicrobial, molecular detection and reporting) which enforces the cluster Advanced Materials in the KIA Key Technologies
- Design and synthesis of new (bio)molecular entities which enforces the cluster Chemical technologies in the KIA Key Technologies
- Through this Chemistry of Life roadmap, new sources of e.g. proteins are currently being implemented and food is improved chemically which requires a detailed molecular understanding of (plant) cellular mechanisms to support the mission of feeding the ever-increasing world population in a sustainable manner which is also addressed in the KIA LWV and the KIA Circular Economy. Chemistry is instrumental 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 and supports the related missions formulated in the KIA LWV and the KIA CE
- Less spoilage of foods as formulated in the missions of the KIA LWV and the KIA CE by exploring biochemical production and use of new nature inspired preservatives,
- The chemical knowledge generated for diagnostics and the information on the chemical status in a body contributes to the KIA Health & Care, mission I (lifestyle and environment) and mission III (chronic diseases).
- Designer minimal cells for application and production in bioenergy, biomaterial and (bio-)chemical production as described in pillar 3 of this roadmap support 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.
- Cell like entities as smart diagnostic and therapeutic agents as described in pillar 3 of this roadmap contribute to the improvement health and healthcare the overall aim of the KIA Health & Care.

Connections / Cross Overs

The Chemistry of Life program has been initiated to strengthen the collaboration within the different programs of TKI Chemistry as well as across the different TKIs. This is important as we realize that innovation doesn't happen is silos (competing for limited resources) but at the interface of different disciplines and by multi-disciplinary contributions and collaborations (sharing limited resource).

While the current roadmap has been designed from the identified specific needs and opportunities in Chemistry of Life, it is not surprising that many desired connects exist with other TKIs and EU initiatives. Some of these connections are presented in table 2 which shows that all (!) proposed tasks and actions of Chemistry of Live are strongly connected. These connections can be worked out for example in designing joint (cross TKI) calls. In these joint calls the contribution (or knowledge gap) of the different disciplines will become visible and might further guide priority setting driven by specific innovation themes.

Chemistry of Life	**TKI Chemistry**	**TKI LSH**	**TKI Agri/Food**	**TKI Biobased**	**TKI HTSM**	**Horizon 2020**	**Potentially interested companies**
Activity 1.1		-Molecular diagnostics -Imaging			-Diagnostics (incl. imaging)	-Health, demographic change and wellbeing	DSM, Akzo, Unilever, multiple (> 100) start- ups in biotech
Activity 1.2		-Pharmacotherapy -One Health (Antimicrobial resistance)				-Health, demographic change and wellbeing	Synthon, MSD, Janssen, Galapagos, multiple (> 100) start-ups in biotech
Activity 1.3	-Advanced Materials (Materials with added functionality)	-Regenerative medicine			-Enabling technologies (Biomaterials)	-Health, demographic change and wellbeing	DSM, Philips,
Activity 2.1			- Proteins, Carbohydrates, Oils			-Food security, sustainable agriculture	FrieslandCampina, Unilever, AVEBE, Danone, Cosun
Activity 2.2		- Specialized Nutrition Health	- Roadmap health (e.g.			-Food security, sustainable agriculture	FrieslandCampina, Unilever, AVEBE,

		and Disease	healthy aging)			-Health, demographic change and wellbeing	Danone, Nestlé
Activity 2.3	- Chemical conversion, processes and synthesis (Biomass and renewable resources)		- New adapted feedstock -Ligno-cellulose as feedstock	- Bio-refinery: Proteins, oils, carbohydrates separation, nutritional and pharma products from plants		-Food security, sustainable agriculture -Climate action, environment, resource efficiency and raw materials	FrieslandCampina, Unilever, AVEBE, Danone, Nestlé
Activity 3	- Nanotechno-logy (e.g. energy storage) - Chemistry & Physics; Fundamentals for our future, Rapport Commissie Dijkgraaf	- Regenerative Medicine - Enabling Technologies	- Roadmap health (e.g. metabolic programming)	- Solar capturing (incl. micro-organisms)		-Health, demographic change and wellbeing -Food security, sustainable agriculture -Secure, clean and efficient energy	

Table 2

Task 1: Molecular entities, devices and approaches for understanding, monitoring and improving precision healthcare

1.1 Development of analytical, biophysical devices and cellular model systems

1.2 Creation of new chemical, molecular and cellular entities

1.3 Biomedical Materials for improved functionalities

Task 2: Molecular entities, technologies, devices and approaches for understanding, monitoring and improving food to ensure a sustainable supply of safe and nutritious, delicious food and feed to optimize health and wellbeing

2.1. Biochemical tailoring of food

2.2. Understanding food digestion and metabolism to increase nutritional availability and health

2.3. Sustainable production and consumption

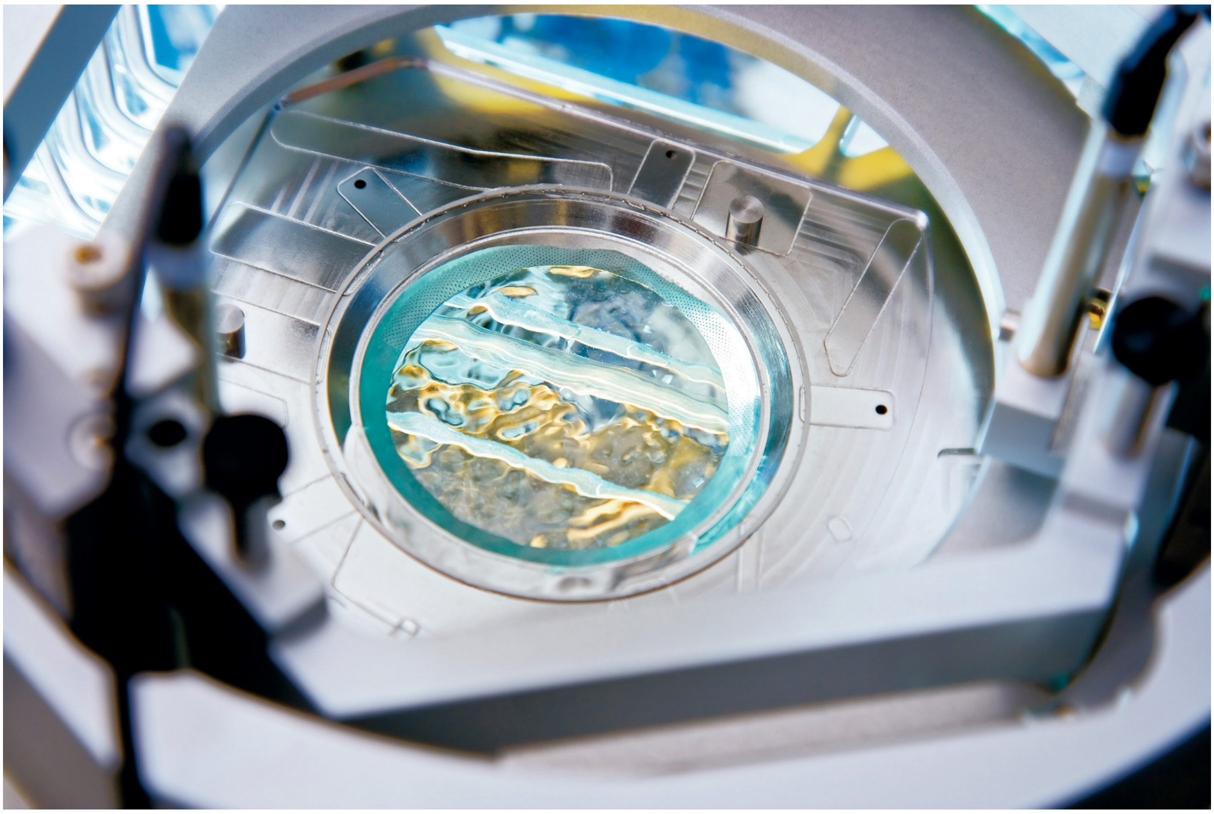
Task 3: Enabling technologies and approaches for fundamental understanding, monitoring and improving molecular entities in the Chemistry of Life

3.1 Understanding of cellular processes from molecule to organism

3.2 Engineering of molecules and cells

ChemistryNL

Roadmap
Chemical Conversion, Process Technology and Synthesis



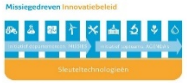
Content

Executive summary

Making sustainable chemical products

On top of the list of Global Challenges we find the need for sustainable development and the necessity to address the climate change. High on the list as well is the Global Challenge to sustainably meet the growing energy demand. The field of chemistry is ready to take on a key role in helping to tackle these challenges. At the same time, it will have to deal with the changes these global developments will impose on the sources of raw materials and energy which have been the basis for the chemical industries for many decades. In particular, catalysis, process technology and synthesis are crucial disciplines when it comes to establishing the scientific and technological foundation for making cleaner, more efficient, economically viable chemical production processes, and enabling a change in feedstock and energy sources to fuel our processes.

In this document, the program council describes how circularity and the use of bio-based feedstock will play a more and more important role. It addresses how it will use catalysis and process technology for the production of functional molecules, materials and (precursors for) energy carriers, making use of the current and future feedstock and energy sources. With the strongholds for these fields of expertise in the Netherlands, it is indicated how reactions, catalyst materials, reactors, and production processes shall be integrated at all length- and time scales of importance. These aspects jointly will be instrumental in retaining the competitive edge of chemical industry and catalyst industry in the Netherlands. The overarching ambition for the year 2050 is to complete the transition from our fossil resource dependent economy to a circular low-carbon economy that relies on sustainable and abundant resources. A roadmap is presented that includes chemical technologies to realize this ambitious goal.

	Energy Transition and Sustainability			Agriculture, water and food	Health and Healthcare	Security	Key Technologies	Societal earning capacity
ChemistryNL Roadmap 	Climate and Energy (IKIA) *in particular Mission C "Industry"*	Circular Economy	Future Mobilitysystems	7 missions	4 missions	8 missions	Key technnology (ST) clusters: ChemTech, AdvMat, DigTech, EngFabTech, LifesciTech, NanoTech, PhotoTech, QanTech	3 tracks
Chemical Conversion, Process Technology & Synthesis							ChemTech, EngFabTech	
Making molecules efficiently	efficient use of heat in MMIP 7 use of electrocatalysis in MMIP 8	CO2, N2, H2O as feedstock in Mission 2						
Making molecules circularly	Chemical recycling in MMIP 6 Use of renewable feedstock in MMIP6 Use of renewable fuels in MMIP9	Circular design in Mission 1 Chemical recycling in Mission 2 Use of renewable feedstock in Mission 2		Use of organic waste streams in Mission A			Process technology, Catalysis, Process Technology in ST1 and ST7	
Making functional molecules								

1 Introduction

The scientific knowledge generation supported by ChemistryNL serves two purposes. Societal challenges on the one hand call for focused innovation while scientific challenges require a strong basis of the underlying (chemical) disciplines. Both goals are highly complementary and form the basis of the next two chapters.

The societal challenges are described in chapter two and are divided into three themes:

- *Making Molecules Efficiently*, which focuses on creation of efficient (minimal resources using) processes per sé (large volume products are dominant application field).
- *Making Molecules Circularly*, which focusses on, as high as possible, re-use of molecular material, supplemented (if necessary) by bio-renewable feedstock.
- *Making Functional Molecules*, which focuses on creation of new (societal relevant) functionality in molecules, includes methods of preparation (specialty, fine and pharma chemicals are dominant application field).

The scientific and technological challenges are described in chapter three and are divided into three disciplines:

- *Process technology*
- *Catalysis*
- *Synthesis*

The roadmap promotes multi-scale understanding and developments all the way from active sites (nm), particle agglomerates (µm) to catalyst particles (mm), to reactors (m) and the refineries or chemical plants in which they are integrated, as well as the time-scales governing chemical reactions (ps) via transport phenomena (ms) to the complete lifetime of a catalyst (minutes to years). Interdisciplinary research where all these scales are combined have proven useful in optimizing particular systems. In addition to the dimensions, understanding how these existing (infrastructural) systems are linked also yields valuable information. Understanding these systems can help to find the right approaches to enable the energy and material transitions that we currently face. This is especially true for developments where materials that have been used as an energy source are now recycled to serve as feedstock. Such chemical knowledge can be used in transdisciplinary research that are the basis for new policy that target system wide changes.

The contents of the roadmap fits into the program of Horizon Europe. It has a good overlap with Horizon Europe's Cluster 4 (digital, industry and space). Relevant calls can be found in themes like manufacturing technologies, circularity of resources, electrification and climate-neutral industry. The main purpose of this roadmap is to structure funding in national innovation programs. The previous version of this roadmap was a base for the knowledge and innovation agenda’s (KIA), now the contribution of this roadmap to these KIA's is stressed.

1.1 Why should we do this?

The continuous growth of the world population cause issues such as a huge increase in demand for energy, clean drinking water and consumption goods. To meet these demands and at the same time reduce the use of fossil resources, or even more so, transform to a CO_2 neutral industry and society presents huge challenges and calls for breakthrough innovations. Chemical research and chemical industry will play a key-role in the transition that our society has to make.

Creating a sustainable energy supply with minimal use of fossil fuels and making our industries circular by using sustainably sourced raw materials are some of the most important challenges at this time.

Meeting these challenges will be essential to ensure a healthy future for the world population, to preserve biodiversity and protect our planet.
The climate treaty of Paris has been an international effort to limit global warming and has led to European and national initiatives. Europe is striving for a climate neutral economy in 2050 by implementing the Green Deal with the first milestone set in 2030. The Netherlands has formalized this into the raw materials and climate accords (grondstoffenakkoord en klimaatakkoord) with similar deadlines.

1.2 How is this relevant to the Netherlands?

The research directions proposed in this document relate to the Missions as described in the Knowledge and Innovation Agenda. They will contribute to more efficient use of resources, resource recycling, reduction of waste and CO_2, and conversion of waste to useful raw materials. It will create (higher educated) jobs, and promote resource independence, as well as novel sustainable routes to biomedical, food, feed, fertilizers and specialty products. It will lead to increasing use of progressively lower cost sustainable resources, and improve European competitiveness towards Asia, USA, and the Middle East.

The Chemical industry in the Netherlands generates an approximate annual revenue of 64 billion euro, and with this, the Netherlands is the fourth largest chemical producer in Europe and tenth worldwide. About 46,000 people are employed in the chemical industry (source: CBS). The Netherlands combines its strong process industry with a concentration of catalyst and enzyme producers, the importance of which is clear from the fact that about 85% of all chemicals are being made through catalytic processes. The Industrial players are closely involved with the Dutch academia which are traditional strongholds in the fields of catalysis, (bio)catalysis, organic synthesis, process engineering and downstream processing. Synthesis of functional materials (e.g. bioactives developed in SME's), and polymeric materials (through homogeneous or heterogeneous catalysis or fermentation), is a strongly developed field.
Academic research in the Netherlands in the mentioned fields is of world class status. Industry involvement in academic research is demonstrated from the active participation in public-private-partnerships. PPP's with multiple industries involved are much less untypical in the Netherlands than in the countries surrounding us, enabling programs that can lean on broad support.

In addition to the above, the infrastructure in the Netherlands is ideally suited for the realization of a circular economy. The infrastructure in the ARRRA (Antwerp-Rotterdam-Rhine-Ruhr-Area) cluster is well equipped to handle large amounts of biomass (wood and straw type). The agricultural knowledge provides very high production yield crops (e.g. 15 ton sugar per acre). The combination of sea ports, green energy (electricity) supplying providers and big refineries give the energy integration as required for successful biorefineries but also for electrified chemical processing.
The characteristics of the chemical landscape, as is illustrated in the above, makes it obvious that investments in research and innovations in this field is of great importance. Not only does The Netherlands have the right infrastucture to be successful in these innovations, but such investments will at the same time be of key importance to maintain our industry to be successful and competitive. It will be the only way to guarantee this sector to make the transition to sustainable processes and to meet the goals as have been laid down in the climate treaty of Paris the raw materials and the Dutch climate accords (grondstoffenakkoord en klimaatakkoord).

2. Overview of themes

2.1 Making molecules efficiently

In 2050 the majority of chemicals are no longer synthesized with the use of fossil fuels. Chemists and chemical engineers are striving to produce molecules more efficiently both in terms of greenhouse-gas reduction and efficient material use. Also biotechnological approaches are being pursued. Efficiency goals are set for both greenhouse-gas reduction and material use. The greenhouse gas reduction goal for the Dutch industry is 59% CO_2 eq reduction in 2030 compared to 1990 and climate neutral production in 2050, as described in the industrial part of the Dutch Climate Agreement (klimaatakkoord, deel C). Approximately 50% circular production of plastics is anticipated by 2030-2040. The final goal is that by 2050 we have established a complete circular economy (grondstoffenakkoord). These goals are rather ambitious and require the implementation of research advances in an industrial setting on a short term.

At industrial level we define three categories of actions to produce molecules efficiently:

1. Development of efficient production routes (choice of fundamental conversion steps (info from synthesis and catalysis disciplines), choice of reactor and separation concepts)
2. Integration of heat pump technology and heat network optimization, control optimization, insulation optimization, industrial symbiosis, and regional heat networks to increase efficiency
3. Decarbonization of energy carriers, by means of CC(U)S (carbon capture, utilization and storage) and renewable energy

These categories are interlinked and can strengthen each other, but are surely not mutually exclusive.

Developing efficient production routes

Developing efficient production routes requires the type of technology development as described in MMIP 8. (Elektrificatie en radicaal vernieuwde processen).

The relevant chemical key technologies are (bio-)process technology (ST[1] 1-1), (bio-)catalysis ST 1-3 (ST 7-1), Electrochemistry/E-refining as well as high temperature process electrification and integration (ST 1-4), Innovative reactor design and Microreactors (ST 1-5) and separation technology (ST 1-6).
The Dutch industry is in general built between 1965 and 1985. Consequently, the technology applied is technology that was already proven in 1970. In the meantime, new insights are gained on how to produce more effectively.

The key chemical technologies listed above enable us to completely redesign factories allowing us to significantly reduce energy use that is presently necessary to separate main- and by-products by assuring that a reactor only produces the required product within spec without the need of upgrading the product streams by means of a combination of separation technologies. Or it allows us to replace a separation unit by more energy efficient technologies.

Developing efficient production routes is not only relevant to increase the production efficiency of current production facilities, but also for the production facilities that are being developed in order to produce circularly as described in MMIP 6. To balance the energetic and the material efficiency it is important to reduce the production of CO_2 as much as possible. Subsequently this calls for maximum molecular valorization of other carbon sources such as plastic waste streams, biomass, CH_4 as well as CO containing streams. If it is required to convert CO_2 to useful hydrocarbon molecules it is important to make sure that the reduction of oxygen is carried out as energy efficient as possible, instead of applying hydrogen that is produced using electrolysis. This approach is the very basis of MMIP 13. (Een robuust en maatschappelijk gedragen energiesysteem).

[1] A number of key technologies have been defined, an overview can be found in the appendix.

Efficiency steps

The technologies required to carry out the steps in this category are in principle known: heat-exchanger network-optimisation, heat-pump-technology and heat-transformer integration, insulation and control optimisation, industrial symbiosis, and regional heat networks. The challenge is to apply this knowledge in an integral way to minimize energy use and maximise material efficiency. Furthermore the range of temperatures and temperature-lifts that can be enabled is to be pushed higher. Experience with lesser known principles like Stirling motor as a compression principle have to explored. The identification and thermodynamic characterization of climate safe working media that are adequate at high temperatures deserves further attention.

The outcome of the application of these efficiency steps allows for the most cost effective part of MMIP 7. (CO_2-vrij industrieel warmtesysteem) and contributes to MMIP 13. (Een robuust en maatschappelijk gedragen energiesysteem).

The key chemical technologies are heat-pump technologies like MVR, high temperature heat pumps (ST 1-4), heat transformers (ST 1-1/ST 5-4) .

Decarbonisation of Energy carriers, by means of CC(U)S, renewable energy

Decarbonisation of Energy carriers, by means of CC(U)S, renewable energy to realize the goals described in MMIP 7 (CO_2-vrij industrieel warmtesysteem) and contribute to MMIP 13. (Een robuust en maatschappelijk gedragen energiesysteem). The research goals in this category are in the field of system integration. Chemical key technologies are Electrification / Hydrogen Technology / Power to Gas (ST 1-4) and Separation Technology (ST1-6).

The challenge is that a large part of the national energy consumption is consumed by industry and that this industry is designed to produce on a very large scale, continuously 24 hours a day for years without interruption. This was possible by an endless supply of carbon fuels.
The second challenge is to valorise the quality of the energy sources applied to their thermo dynamic optimum. Although the total amount of energy is by definition constant, the potential to do work reduces when applying electricity in low temperature applications.
Decarbonisation of this energy supply is for a limited number of years possible by capturing the CO_2 and storing it in depleted natural gas fields. This storage capacity is limited but offers a way to drastically cut emissions on the short term.
Separation technologies reducing the energy intensity and increasing the quantity as well as the purity of CO_2 captured, are very important because the capture of CO_2 still requires a lot of energy.

For the long term the challenge is to connect the industry with its enormous continuous energy demand to the less continuous supply of sustainably harvested renewable energy. Part of this connection will require a significant lowering of this energy demand as described under “Developing efficient production routes”, partly by increasing the flexibility of the processes, partly by converting electricity into energy carriers that can be stored more easily.

Expected results present – 2050

Societal goal:

- climate neutral in 2050 (klimaatakkoord)
- circular economy in 2050

Milestones:

- greenhouse gas reduction goal for the Dutch industry is 59% CO_2 eq reduction in 2030 compared to 1990 (klimaatakkoord, deel C)
- approximately 50% circular production of plastics by 2030-2040.

Industrial end goal:

- climate neutral production in 2050 (klimaatakkoord, deel C)
- circular production of plastics by 2050

2.2 Making molecules circularly

In The Netherlands, the majority of carbon-based chemistry starts with naphtha cracking. To be able to have drastic reduction of the CO_2 footprint, circular concepts are needed that can reduce the amount of naphtha required. These concepts can be related for example to polymers, biomass, metals and carbon dioxide itself.

Circular polymers

The current situation on polymer recycling relies on two main approaches: mechanical recycling (aimed at winning the material back from waste streams) and chemical recycling (mainly aiming at winning valuable chemicals, including monomers whenever possible, by (thermo-)chemical depolymerization of the polymeric chains). From a scientific point of view, four main topics still require particular attention in terms of developing new concepts on a fundamental level:

I. recycling of crosslinked structures (rubbers and thermosets);
II. improvement of molecular efficiency of chemical recycling by catalysis & electrification;
III. upgrading the current recycling approaches for thermoplastics suffering relevant side-reactions during processing (for example degradation);
IV. combining different waste streams into polymer blends possibly to be optimized via reactive extrusions strategies.

These main topics tap into most steps of the circular value networks/circles that need to be created out of the current linear value chains: collection, sorting, separation, recycling, production and use-phase. Integration of the “supply chain” for waste materials both from postconsumer as well as industrial streams seems to be a condition sine qua non in order to define, among others, decision models for the allocation of given waste streams for mechanical and/or chemical recycling.

In general, significant advances are required in the collection, sorting and separation of waste streams (for example in the field of sensor technologies and Artificial Intelligence for data & image processing). After collection and physical separation, meticulous characterization is needed in order to identify the impurities remaining in the material. Low molecular weight compounds should be identified as to propose suitable separation techniques (both before and after collection and physical separation), which should then be attractive at industrial scale. This might disclose on the longer term application of relevant streams for added values applications where the absence of any unwanted impurities is paramount, both for mechanical as for chemical recycling strategies. On the other hand, in case the pollutant is another polymer, identification of the kind of material (simple polymer blend as opposed to co-polymers) is crucial in devising further strategies. A simple blend can in principle still be separated in individual components although the classical approach (at academic level) of selective solvent extraction is clearly not suitable at industrial level and new more efficient and less energy demanding strategies should be defined and researched.

In view of CO_2-reduction, molecular efficiency of the (chemical) recycling technologies is of paramount importance. With a low efficiency, waste is generated, or the carbons are utilized as energy source (with CO2 as a consequence). Fundamental research on the use of (heterogeneous) catalysis combined with electrification strategies (microwave, plasma, electrons/photons) for the depolymerization of plastics into monomers (feedstock recycling) is required, focused on carbon recycling.

For composite materials, without a chemical bone between the matrix and the filler, selective separation could be deployed. On the other hand, a copolymer cannot per definition being simply separated in the individual blocks. Straightforward application of these materials as compatibilizers for polymer blends might be then considered a valuable option that dovetails strategy III (vide supra). Identification of other application routes for these copolymer should be further investigated.

Last but not least, when dealing with post-consumer waste, it is worth noticing how the relative production volumes still point to a few classes of polymers (polyethylene, polypropylene, poly(vinyl chloride), polyethyleneterephthalate, polystyrene etc.) as the major contributors, in volume, to the waste. In this context, it would be strongly desirable that the research points and strategies outlined above would also, if not predominantly, be referred to this class of bulk polymers.

Circular critical elements

Conservation of our elementary building blocks is needed to ensure their application in sustainable technologies, prevent chemical pollution and preserve biodiversity. This can only be carried out by recovery and recycling them after their use. The development of chemistry that enables the circular use of our elements, molecules and materials is therefore key, next to preventing chemicals from entering the environment, and thus avoiding them to cause pollution. Safe and circular by design of molecules and materials for a sustainable future is thus of utmost importance. Inducing such change from the current linear 'take-make-dispose' model to a more circular one requires a holistic approach to design a new system of using and reusing our precious elements.

The Critical Raw Materials List (CRM) of the European Commission contains 30 materials (Antimony, Baryte, Beryllium, Bismuth, Borate, Cobalt, Coking Coal, Fluorspar, Gallium, Germanium, Hafnium, Heavy Rare Earth Elements, Light Rare Earth Elements, Indium, Magnesium, Natural Graphite, Natural Rubber, Niobium, Platinum Group Metals, Phosphate rock, Phosphorus, Scandium, Silicon metal, Tantalum, Tungsten, Vanadium, Bauxite, Lithium, Titanium, Strontium), of which the last four are added in 2020 to the list for the first time. In the coming years, the availability of those critical raw materials is under stress and the mining will eventually reach peak production, like it was already observed for oil in some countries. Recovery and recycling will become more important and (bio-)chemical recycling techniques will be required.

Many scarce metals and materials are critical for the Dutch and EU industry, in particular for the high-tech and clean energy applications. Examples of these critical materials include: rare earth elements in particular neodymium (Nd) and dysprosium (Dy) in permanent magnets for electric motors/generators in wind turbines and electric vehicles; cobalt and lithium for Li-ion rechargeable batteries for electronic products/equipment and electric vehicles.
Industrial recycling value chain involves three interconnected steps: collection, physical separation, and chemical/metallurgical refining. At present, The Netherlands is among the front runners of the collection system and infrastructure for most of the waste and end-of-life (EOL) products, and has quite mature physical separation industry with advanced technologies such as ARN for collection and physical (or mechanical) recycling of EOL vehicles or ELVs, Renewi and SIMS recycling for physical recycling of electronic waste. However, there is a clear knowledge and technology gap for efficient separation and extraction of these critical materials. The main challenge lies in their dilute use as "minor constituents" in the bulk materials (e.g. minor alloying elements, coatings), or relatively small or tiny components in a large equipment or product.

Biochemical elements like carbon, nitrogen and phosphorus face different challenges. The disposal of these elements have pushed four of the sustainability targets (Steffen, Rockstrom et al. Science 2015, 347, 736) into unprecedented territory, namely: extinction rate (one of two indicators for biosphere integrity), atmospheric carbon dioxide (an indicator for climate change), and the biogeochemical flow of nitrogen and phosphorus, of which the latter three can be solely ascribed to the chemistry of three elements: (C, N, P). Urgent action therefore needs to be taken to return to safe operating space in these processes.

Therefore, next to advancing resource management, sustainable chemistry is also urgently required to tackle environmental waste issues. For carbon, this mainly concerns the greenhouse gases carbon dioxide and methane that are expelled to the atmosphere. The nitrogen waste issue is caused by nitrogen oxides (N_2O, NO_x) and predominately ammonia (NH_3) that are discharged into the aquatic environment and/or atmosphere. For phosphorus, it concerns phosphate, which is next to ammonia essential for plant growth, yet this building block of life also ends up in aquatic systems causing eutrophication. Ironically, C, N, and P are key players in the suite of major biogenic elements, often termed 'CHONPS', needed in large quantities to make living organisms, but also contribute heavily to three of the most stringent environmental concerns.

Use of biomass

Bio-based feedstock (e.g. biomass) is a renewable (sustainable) heterogeneous resource consisting of functional molecules (polysaccharides, lignin, proteins, lipids) formed by nature out of CO_2, water, nutrients and sunlight. Bio-based feedstock are used since the dawn of mankind for e.g. food, feed, heat and construction materials. More recently it was realized that bio-based feedstock could also be a sustainable source for chemicals, fuels and materials like polymers. However, care has to be taken that its use for these purposes does not compete with its use for food and feed (i.e. the food vs fuel discussion), and thus contributes to further conversion of nature to cropland (land use change), a major contributor to biodiversity loss.

To make efficient use of the molecules present in bio-based feedstock, a biorefinery approach to efficiently separate the different components and, when needed, convert them further to the desired products, is needed. When doing so three prerequisites have to be satisfied:

1) do not endanger food/feed production;
2) use the feedstock to its highest value;
3) make molecules/products which can be recycled (i.e. connect to a circular economy) or that replace fossil-based products that cannot be recycled (e.g. paints, coatings, lubricants, rubber, etc.).

Although examples exist of high TRL biorefinery approaches and of products that even made it to commercialization (e.g. polylactic acid), the large scale use of biorefinery approaches which can outcompete the large scale use of fossil resources in an oil refinery is limited. This is mainly related to the low yields, high energy inputs and too specific approaches for each bio-based feedstock which all relate to the complex nature of bio-based feedstock. Here clear improvements need to be made. This does not only require new scientific and technological breakthroughs, but it also requires new value chains in which 'unconventional partners' like bio-based feedstock producers, food industry and chemical industry collaborate.

To achieve the use of bio-based feedstock on a large and economically viable scale different steps need to be made:

1) Application of novel (bio-)catalytic processes that reduce the high energy inputs and increase the yields of biorefinery operations, whilst working with a variety of (less pure) bio-based feedstock. Since (bio)catalysis is a core element it will be discussed separately.
2) Development of new biorefinery and separation technologies to produce products based on their required functionality rather than on their purity. This is expected to result in lower energy input and less processing steps.
3) Development of new value chains that use bio-based feedstock without endangering food/feed production.

Circular carbon

The last 10 years significant progress have been made in creating basic knowledge on the conversion of CO_2 into value added materials. CO_2 could be one of the carbon sources of the future. Materials and chemicals by 2050 will be most likely heavily based on carbon, therefore, the use of CO_2 as a circular carbon source is of interest. The challenges related to the conversion of CO_2 are:

- energy efficient conversion and highly selective conversion integrated with adequate separation technology
- integration with renewable energy landscape
- modular and smaller scale process units
- integration with CO_2 capture

Electrochemistry, catalysis, biotechnology and photochemistry will be relevant for the development of suitable conversion methodology. CO_2 utilisation can benefit from large scale renewable electricity production. Nevertheless, continuous life cycle assessments are needed to judge the sustainability of the conversion method.

Expected results present – 2050

Societal goal:

- Demonstrated integrated polymer recycle concepts based on physical and (bio)chemical recycling methods
- Creation of new technology cradle to cradle chains which could be integrated into the current polymer producing industry
- Demonstrated conversion routes for maximum recovery of all fractions' biomass value (targeting from high-value products to fuels and energy).
- Demonstrated CO_2 conversion processes, related to the production of specialty chemicals
- Security of supply dilemmas (e.g geographic) of key metals de-risked

2.3 Making functional molecules

There is an obvious major demand for, and push to, more efficient and lower footprint chemical processes. To a large extent this relates to already existing molecules with an existing function. It should however be realized that the current set of industrial scale molecules is largely based on a historic context: derived from (easily) available fossil raw materials and with the function mostly discovered by empirical testing. In the coming decades the necessity to introduce molecules on industrial scale -) with a pre-requested and designed function and -) based on renewable/recyclable raw materials, is eminent.
This holds for small molecules as end product: e.g. 'customer-oriented functionality' such as drugs, crop protection agents, flavor & fragrance, dyes, as well as for all kind of 'industrial-oriented functionality', such a lubricity, anti-oxidation capacity , repellency etc.
It also holds for small molecules that act as monomer for (new/adapted) polymeric materials, current relevant examples include : furandicarboxylic acid (FDCA), lactic acid, isosorbide.
Making functional molecules thus has 2 major thrusts: a strong enabling character for new molecules, but also as source for new technologies to improve processes.
Therefore 'making functional molecules' connects to the efficiency/footprint MMIPs (Sluiting kringlopen, Electrificatie en radikaal nieuwe processen, Ontwerp voor circulariteit, en Circulaire grondstoffen en productie processen), to 'Hergebruik organische zij- en reststromen', as well as the STs required.
The discipline 'Synthesis' (chapter 3) is at the heart of making functional molecules. However, this is always in interplay with 'Catalysis' and 'Process technology' (chapter 3). The connection with missions, tasks and disciplines from other Roadmaps needs to be mentioned. Depending on the business field (e.g Life Science molecules or (polymeric) materials) the strongest connection will be with different other Roadmaps.

Expected results present – 2050

Societal goal:

- Demonstrated relevance of biobased and recycled streams for high performance materials and chemicals including concrete examples of this approach
- Cost-effective end products with lower environmental impact of chemical manufacturing (measured against internationally consolidated measurement system)
- Conservation and creation of knowledge-intensive jobs in the fields of the manufacturing of special/fine/pharma chemicals as well as high performance materials
- Intrinsically safe and resource and energy efficient production of fine and specialty chemical molecules/products.
- Security of supply dilemmas (e.g geographic) of key complex chemicals de-risked.
- Simplified logistics / shorter supply chains

Industrial end goal :

- Fully integrate waste, recycled and biobased streams in the monomer selection step for chemical product design.

- Sustainable and robust manufacturing of any required end product through catalytic processes using abundant and renewable raw materials;
- A leading position of the Netherlands and Europe in the production and supply of fine and specialty chemical molecules/products as well as high performance materials

3. Overview of disciplines

3.1 Process technology

As mentioned in the previous chapter there are two very demanding ambitions set to make process industry more sustainable:

- climate neutral in 2050
- circular economy in 2050

The discipline of Process Technology (PT) will play an important role in implementing the innovations required to realize these goals. We will describe more in detail the envisioned progress in four disciplines of PT: transport phenomena, reactor engineering, separation technology, and process systems engineering.

Transport Phenomena
Advancements in the area of transport phenomena, including powerful computational techniques, high-resolution measurements, and the increasing availability of time-resolved data sets, will continue to support the development of chemical processes in the coming decades. A detailed fundamental understanding and control of the transport of species (small molecules, biomolecules, ions, particles, cells) and energy (heat, light, etc.) at multiple length scales remains crucial for the deployment of new technologies. For instance, emerging technologies for (electro)chemical conversion are dominated and limited by new types of physical transport phenomena which are not considered in the “classical” chemical engineering toolbox (e.g., electrokinetic transport). Careful consideration of such transport limitations are essential for scaling up strategies. Similarly, novel processes based on biomass as feedstock require improved understanding of multiscale transport phenomena of large molecules and molecular aggregates/complexes in (bio)reactors, with dramatically decreased mobilities/diffusivities and increased sensitivity of the transport and material properties of local temperature. Moreover, there is an increasing interest in development and usage of complex bio-based materials, which requires further development of multiscale methods that can link molecular structure and transport to macroscale material properties. While gas and liquid flows have already been studied for decades from first principles, the field of multiphase flow has remained rather empirical. Novel algorithms, strongly increased computational power, and advanced measurement techniques (such as tomography with high temporal & spatial resolution) will enable the extension of rigorous description of transport phenomena in powder flows, bubble flows, emulsions etc. Finally, the development of transport phenomena for micro- and nanosystems will be crucial to support sectors such as the micro-electronics and nano-medicine. In such systems, we often operate near the boundary between a continuum and a discrete description, which requires a dedicated approach.

Reactor Engineering
The upcoming transitions in the process industry also have important consequences for chemical reactor engineering as a discipline, and require novel research directions in this area. A more intermittent energy supply and more varying feedstock will enforce that reactors can deal with dynamic operation and complex flows. Process intensification will remain in important area, developing reactors that have integrated other functions, such as separation, next to the chemical reaction. Novel ways of supplying energy to reactors (electrocatalysis, photocatalysis, plasma, high-gravity) will find their way from the laboratory to industry. Structuring of reactors will increasingly be applied, since this can either boost the efficiency (e.g., higher mass transfer) or because the energy supply requires this (e.g., electrode plates). 3D printing and other additive manufacturing approaches to make reactor internals or complete reactors will become increasingly important, as well as the treatment of these surface to optimize their functionality (catalytic, self-cleaning, etc.). In an increasing number of cases, the distinction between catalyst particle and reactor will vanish (like it is already the case for the three-way catalyst). In some sectors, such as the pharma industry, the transition from batch to continuous processes will continue. A gradual transition from bulk chemicals to high-value materials (e.g., nanostructured products) with varying properties will require the development of novel, more flexible reactor types. Renewed attention for scale-up approaches will be required, as for certain reactors types (electrolysers, micro- and millifluidic systems) simply enlarging the volume will not work.

Separation Technology
For high volume production applications approximately 50% of the total production costs are needed for separations, so the applied technology is a very important aspect in a wide range of industries, such as the energy sector, the water sector, the chemical industry, and agro, food and feed. The main challenges for the discipline include: 1) Reducing as much as possible the dependence on fossil fuel as carrier of the energy converted into the thermodynamic separation work, in order to also reduce the emission of CO2 and other greenhouse gases. This may be achieved by approaching the thermodynamic minimum energy demand as close as possible, for example through smart integration of heat transfer operations, which may include heat pumps. Alternatively, by using a more sustainable driving force (e.g., electric driving forces powered by green electricity). 2) Becoming more flexible and able to handle streams with an increasingly complex nature, as required by the circular economy ambitions. These have a variety of origins such as in recycle- and bio-steams, and flexibly handling such complex streams that vary in composition from day to day may be addressed using modular fractionation strategies, where parts of unit operations can be switched on and off easily and without large losses.
Another important area is the separation of delicate high value molecules such as proteins, vitamins and antibodies, which should very selectively be separated under very mild conditions to to preserve their properties and value. Such surgical precision separations are applicable to a range of high-value products in food processing with an increasing focus on nutritional value, as well as in (bio) pharmaceuticals and agrochemical applications.

Process Systems Engineering (PSE)
PSE develops methodologies to support decision-making in a complex environment to optimally plan, design, operate and control chemical processes. For a truly sustainable technology the decisions should be based on economic, ecological and social implications. The boundaries of the system can be chosen different in space (a chemical plant, an industrial complex, a company, the industry, ..) and time (tomorrow, a quarter, plant life time ..). PSE contributions and developments in five areas are foreseen: 1) smart process modeling where the concept of artificial intelligence, coarse-graining, and digital twinning is fully used, 2) uncertainty assessment including advanced data analysis, 3) multi-criterion decision-making, 4) algorithmic solution methods that can be used to design and operate the future interconnected process systems 5) the overall integration, the implementation, sharing and valorization of the tools via the creation of human capital.
Heat remains a very important area of attention. It represents 80% of present industrial energy use. A thorough understanding and insight in this field beyond the classical pinch is essential. This can lead to the direct use of electrical power for high temperature processes and subsequent energy extraction through power generation combined with lower temperature heating medium.
Future process automation will need to be adaptive, because of varying feedstock mixes, energy supply profiles as well as more specific and tailored demands from markets. The boundary between batch and continuous processes will blur and process automation and safeguarding will have to perform in any state the process is in. This will call for multi-level and dimensional data integration from physical equipment to anyone in need of interaction with the process with full data integrity and security. AI, VR, AR will play ever increasing roles in areas such as direct operations, training, safety, maintenance, quality and reliability.

Expected results present – 2050
Scientific/technological goal:

- Versatile multi-scale modelling approaches and high-resolution measurement techniques facilitating smooth translation from lab/pilot-scale to industrial application.
- A toolbox for developing novel reactor types based on alternative energy input (electricity, light, etc.) and the use of additive manufacturing, including scale-up approaches.
- New technology portfolio of separations working close to the thermodynamic limit and with renewable energy input.
- Digital twin approaches based widely available.
- AI/ML methodologies for process design, control and optimization widely available.

Industrial end goal:

- Climate-neutral chemical industry while being economical with flexibility in operation: being able to deal with fluctuating electricity supply.

3.2 Catalysis

Innovating Catalysis

Key to catalysis has been, and will be, to provide high activity, selectivity and stability in chemical reactions. Also in the field of biocatalysis, new developments on enzyme evolution and incorporation of newly developed enzymes into metabolic pathways pave the way to more efficient biocatalytic manufacturing. (Bio)catalysts need to convert a feedstock with a high rate to decrease reaction time and decrease energy input. (Bio)catalysts need to achieve a high selectivity to prevent additional downstream processing (separation) steps and prevent waste formation. In addition catalysts need to be stable to prevent i) need for increased energy input, ii) frequent reactor shut-down, and iii) the (bio)catalysts themselves to become waste. There will be a large need to develop (bio)catalysts for new, sustainable chemistry and these should meet all these conditions. Therefore a continued research focus will be needed on themes s.a. precise catalyst synthesis, understanding of (bio)catalytic performance and catalyst deactivation. For this tools like operando characterization and computational methods will be further developed.

In addition new challenges can be identified for (bio)catalysis. Most notable are:

- New feedstock
  - With the transition towards a more sustainable society, catalytic processes for alternative feedstock, rather than fossil-based, need to be developed to produce chemicals, fuels, and materials. Biomass and CO_2 are sustainable feedstock allowing production of functionalized hydrocarbons. In the conversion of these feedstock new catalysts, which can cope with these feedstock (and their impurities!) will play a crucial role. Also catalysis allowing re-utilization of waste-streams should be developed. E.g. catalysis for depolymerization of plastics would allow efficient and versatile recycling options, and catalysis to treat the resulting intermediate stream for use in the chemicals value chain.
- Use of alternative stimuli to drive reactions.
  - With the envisioned surplus of renewable electricity, new ways of (combinations of) energy input instead of the currently applied heat, like photons, electrons, plasma, or electromagnetic waves, are expected to become more important in catalytic processing. This requires new catalysts which can deal with (combinations of) these forms of energy.
  - Highly light-efficient semiconductors in combination with suitable, nanoparticulate “co-catalysts” to reduce energy barriers of photon-induced electron transfer reactions, potentially stimulated by heat (photothermal catalysis), need to be developed. Plasmonic particles might allow local, light induced heating, reducing the energy input required for external heating of the reactor. To upscale photocatalytic, photoelectrochemical, or photothermal production routes, efficient reactors need to be designed, either solar exposed, or illuminated by artificial light sources. Gas-solid reactors have been proposed, which allow simultaneous introduction of heat and visible light.
  - Electrocatalysis can bring great opportunities for greening industrially relevant processes. Electrochemistry is of relevance for the production of hydrogen, CO_2 conversion, and perhaps production of ammonia from nitrogen and water. Improved non-noble metal catalysts need to be developed with a long lifetime which allow a high current density and Faradaic efficiency. Integration of the catalysts by advanced system design for electrochemical processing is desired.
  - Solid oxide electrolyzer (SOE) technology is of relevance for producing hydrogen from steam, syngas from CO_2 and steam (so-called co-electrolysis), and CO from CO_2. The main advantage of the SOE technology is that a lower energy consumption is needed for the transformation due to the elevated temperatures. This technology can be further integrated (including by heat exchange) with industrial processes. The challenge is amongst others scaling up and improving durability and reliability.

- Plasma catalysis has recently gained traction, in particular as an alternative to Haber Bosch ammonia synthesis. The current research is mostly fundamental and little attention has been given to the technical and economic feasibility of plasma-catalytic syntheses. The technology appears most feasible for small-scale operation. Plasma catalysis potentially has a fast response to intermittent renewable electricity, and process intensification and integration with other process steps can lead to a further overall improvement.

- New biocatalysts
  Microorganisms and their enzymes offer a multitude of opportunities for biocatalytic manufacturing. Among the big challenges are the identification and engineering of enzymes for synthesis of chemicals and the combination of enzymes into new synthesis pathways to enable the construction of complex building blocks. Processes that combine sequential enzymatic and microbial conversions are also interesting, and could include the use of metabolic engineering. Microorganisms and enzymes can be exploited for the production of natural (or nature-inspired) molecules in the laboratory (and further upscaling to industrial processes). Biocatalysis in combination with electrochemistry also offers novel opportunities, e.g. microorganisms that are able to transfer/receive electrons (e.g. from electrodes) or regeneration of enzymes with bound metals. Microorganisms and enzymes involved in CO2 fixation could play an important for efficient carbon capture and utilization (CCU). Enzymes can also be of great importance in degrading natural compounds (polymers, nitrogen-and sulfur-containing compounds, etc.). They can also be used to degrade recalcitrant compounds like microplastics and micropollutants.

- Traditionally, when designing and developing catalysts with high performance, material restrictions have not been taken into consideration as much as is required by elemental scarcity nowadays. With the increasing scarcity of noble elements, alternative elements need to be found to construct catalytic functionality. Besides innovative screening methodology, also computational design can be of relevance.

- Integration of multiple catalysts and multiple stimuli
  - Often catalysts are designed for a specific conversion. Products are purified and further converted when needed. It would be more efficient when the number of processing steps could be decreased, and catalytic steps can be integrated. That requires new robust catalysts and an integration of the catalysts with the downstream processes. In other words, we need catalysts and reactors which enable process intensification, in particular when multiple stimuli need to be introduced.

To address these new challenges catalysts have to connect to the following key technologies:
- Advanced materials (catalysts)
- Chemical technologies (process technology, analytical technologies, electrification, microreactors, separation technology, nanotechnologies)
- Engineering and fabrication technologies (Additive manufacturing/3D printing)
- Life sciences technologies (biocatalysis)
- Nanotechnologies (nanomaterials, nanomanufacturing)

Expected results present – 2050

Scientific/technological goal:
- <u>Taylor designed sustainable (collaborative) catalysts, allowing application of multiple reaction stimuli</u>
- Advanced (operando) charaterization, understanding of catalytic processes
- New processes where biocatalysts and chemical catalysts are combined in a synergistic fashion

Industrial end goal:
- Catalytic processes for circularity (depolymerization, treating of recycled intermediates)

- Catalytic processes avoiding CO2 formation or based on CO2 as a feedstock
- Biocatalytic processes to produce natural or nature-inspired molecules (difficult to produce chemically
- High selective biocatalysts resistant to feedstock impurities and able to convert mixtures of substrates
- Robust catalytic systems based on abundant metals.
- Precise catalyst synthesis (active phase, texture, shaping).

3.3 Synthesis

Synthesis is the discipline (or competence) 1:1 connected with the various tasks on 'Making Molecules', and through these tasks with the related MMIPs and STs. In fact, the meaning of the word synthesis is the connection of molecules to a new molecule. A very large part of the (Dutch) chemical industry manufactures organic molecules. In creating industrial processes, synthesis is always intertwined with the disciplines 'Process Technology' and almost always connected with 'Catalysis' (certainly for bulk scale processes). For 'small molecules as end products' and monomers for high performance materials, organic synthesis is the key discipline. As a result, organic synthesis is the foundation for other more applied sciences, varying from application field to application field. Analytic chemistry is always involved, and a mix of inorganic-, physical-, polymer-, theoretical-, and/or biochemistry/biotechnology can be relevant. Synthesis already exists for almost 200 years. However, from the perspective of predictability/selectivity, sustainability, and enabling character there are still huge challenges for new synthesis technologies to be developed (both for sustainability/green/footprint as well as functionality-molecular structure correlation perspective).
Synthetic chemistry is the discipline that discovers new reactions in combination with the design and preparation of functional molecules (pharmaceuticals, agrochemicals, food additives, single molecule electronics, photo responsive molecules, homogeneous catalysts). In recent years, we have seen multiple times that the discovery of a new reaction triggered an entire field. The impact of the Cu-catalyzed 'click' reaction and other bio-orthogonal transformations have revolutionized the field of chemical biology. In addition, cascade processes in combination with organocatalytic and photo-redox reactions have shown to be very selective and green. This shows that the discovery of new reactions remains important, either to develop more sustainable processes or to make unprecedented structural moieties and/or functional groups. Although molecules with an impressive level of complexity can be prepared already, still, the efficiency of many of the common synthetic procedures is generally low. 200 Years of synthetic organic chemistry has delivered a plethora of different reactions, far exceeding the transformations that are found in nature. To enable a more efficient and sustainable manufacturing of functional molecules it is important to fully exploit the complementarity of both fields aiming at increasing the selectivity of synthetic transformations and expand the reaction scope of biocatalysis In addition, in the next decades the feedstock for the synthesis of functional molecules will shift from fossil to renewable sources such as agricultural products but also from CO2 reduction and follow up homologation. Therefore, novel methodologies, of which some are discussed below, have to be developed to cope with these green challenges. As a result, in the next decades synthetic chemists will not only be able to design and make even more complex molecules with advanced properties but also manufacture them in a sustainable fashion from biobased materials. With the help of advanced analytical techniques, a deeper insight will gained in "how molecules react" and this will be beneficial for various fields and provide sustainably manufactured highly effective molecules for biology, medicine and material applications. For future novel methodology development and synthesis planning, computational and AI tools are indispensable.
To cope with the challenges that face us in the design and sustainable manufacturing of future functional molecules the following research areas are especially important:

1) Electrochemical synthesis: in fact, synthetic chemistry is the art of taming electrons to carry out the selective formation but also cleavage of chemical bonds. For many reactions stoichiometric reagents are required producing a lot of waste. Directly using electrons as reagents is the ultimate sustainable way to carry out synthetic transformations. Sustainably generated electricity triggers the current revival of developing new electrochemical redox processes. In principle, by using electrons as reagents, the current reagent-directed 'two electrons at a time' mechanisms will be supplemented by 'one electron at a time' radical-type mechanisms opening up new horizons.
2) Photochemistry: photons have been shown for decades their ability to induce the consecutive and selective formation of several chemical bonds providing highly complex molecular structures. In addition to electrochemical synthesis, new photon-induced radical-centered reactions are highly promising as green tools for selective chemical bond formation.

3) Renewable building blocks: lignin derived aromatics, carbohydrates, terpenes, lipids, amino acids are the ultimate starting materials, especially for future functional molecules made in bulk quantities such as base materials for coatings, food additives, monomers for plastics and commodity chemicals. In contrast to oil-derived materials, biobased molecules combine structural complexity with functional group diversity. This requires the development of new regio- and stereospecific synthetic methodology avoiding the use of protective groups and full control of stereochemical aspects.
4) Catalysis in synthesis: The densily chiral biobased materials pose challenges for the metal-centered and organocatalysis fields. Besides showing a high functional group tolerance and stereoselectivity, the future catalysts should be based on non-toxic and abundant metals. Due to rapidly evolving fields of bio-informatics, structural biology and genome editing, tailor-made enzymes can be made to enable selective transformation in non-natural molecules and even catalyze non-natural reactions. The current border between hetero- and homogeneous catalysis that is mainly characterized by the fact the former reactions are carried out in continuous processes and the latter in batch will be faded by flow chemistry. In addition, flow chemistry is highly promising because of the simplicity of upscaling from lab to production scale of the multistep synthesis of complex functional molecules.
5) Supporting tools for synthesis: computational chemistry has become an important tool in studying the mechanistic pathways of chemical reactions. DFT calculations provide additional insight in optimizing chemical transformations improving the predictability both the stereoselective outcome of reactions and reactivity of catalysts. Artificial intelligence (AI) may be of great help in the retrosynthetic analysis of functional molecules. Although search engines for finding specific transformations in the scientific and patent literature have matured, computer-aided retrosynthetic analysis is still, despite intensive efforts in several labs since the eighties of last century, in its infancy. Furthermore, analytical tools such as in situ (or online) IR, NMR and mass spectrometry, with or without connection to UPLC or HPLC equipment, will speed up methodology development. Besides gaining quick and precise structure information, such analytical tools also facilitate the study of reaction kinetics and thermodynamics. AI/Machine Learning (ML) will also accelerate and structure process R&D in 'Making Molecules'.

Expected results present – 2050

Scientific/technological goal:

- Exploit (instead of removing) the functionality present in biobased and/or molecules derived from chemical recycling towards high performance materials and functional chemicals (routine use of bio-based/renewable/recycled chemical building blocks)
- Toolbox of synthetic methods available for the synthesis of complex functional small molecules and catalyst design tools to allow specific 'on demand' activity/selectivity ('Prediction of reactivity' challenge largely solved)
- 'Electrons as sustainable reagents' implemented on large industrial scale
- A toolbox of modular equipment, technologies and sensors enabling the implementation of multi-purpose flexible production systems with reaction, separation and if necessary formulation. The ability to produce functionality on demand (in time and place) by a comprehensive understanding of the relation between process/equipment, molecule and functionality.
- AI/ML methodologies for synthesis route planning and process design and optimization widely available and used.

ChemistryNL

Bijlage A: Chemical Key technologies (Sleuteltechnologieen)

ST 1: Chemical technologies
ST1-1 (Bio)Process Technology
ST1-2 Analytic Technologies
ST1-3 Catalysis
ST1-4 Electrification / Hydrogen Technology / Power to Gas
ST1-5 Microreactors
ST1-6 Separation Technology

ST 2: Digital technologies
ST2-1 Artificial Intelligence
ST2-2 Big Data and Data Analytics
ST2-3 Blockchain
ST2-4 Encryption Technologies / Digital Security
ST2-5 High Performance, Grid, Cloud Computing

ST 3: Engineering and fabrication technologies
ST3-1 (Opto)Mechatronics
ST3-2 Additive Manufacturing
ST3-3 Cyberphysical Systems
ST3-4 High Frequency and Mixed Signal Technologies
ST3-5 Imaging Technologies
ST3-6 Robotics
ST3-7 Sensors and Actuators

ST 4: Photonics and light technologies
ST4-1 Imaging Technologies
ST4-2 Integrated Photonics
ST4-3 Photon Generation and Detection Technologies
ST4-4 Photonic / Electronic Co-integration
ST4-5 Photovoltaics

ST 5: Advanced materials
ST5-1 Bio(related) and Soft Materials
ST5-2 Composites and Ceramics
ST5-3 Designer and Meta Materials
ST5-4 Energy Conversion Materials
ST5-5 Energy Storage Materials
ST5-6 Optical, Electronic, Magnetic Materials
ST5-7 Smart, Self-healing, Self-organising Materials
ST5-8 Structural materials
ST5-9 Thin Films and Coatings

ST 6: Quantum technologies
ST6-1 Quantum Communication
ST6-2 Quantum Computing
ST6-3 Quantum Sensors and Metrology

ST 7: Life science technologies
ST7-1 Bio-catalysis
ST7-2 Bio-chips and Bio-sensors
ST7-3 Bio-fabrication
ST7-4 Gene Editing / Precise Genetic Engineering
ST7-5 Genomics / Proteomics / Metabolomics / Glycosmis / X-omics
ST7-6 Industrial Bio-technology (white)
ST7-7 Nanomedicine
ST7-8 Organ-on-Chip
ST7-9 Stem Cell Technology
ST7-10 Synthetic Cell Technology

ST 8: Nanotechnologies
ST8-1 Bio-nanotechnology
ST8-2 Micro and Nano Fluidics
ST8-3 Nanomanufacturing
ST8-4 Nanomaterials
ST8-5 Nanoscale Devices
ST8-6 Semiconductor Devices

Credits

The contents related to critical elements in the theme-oriented chapter 2.2 'Making molecules circularly' was contributed by Yongxiang Yang (TUD) and Chris Slootweg (UvA).

The contents of the discipline-oriented chapter 3.3. 'Synthesis' was generated by the relevant academic community represented by J. v Maarseveen (UvA), E. Ruijter (VU), J. Codeé (LU), F. Rutjes (RU), A. Minnaard (RUG), and R. Orrú (MU).

Roadmap
Chemical Sensing & Enabling Technologies

Roadmap
Chemical Sensing & Enabling Technologies

Enabling & sensing technologies for chemistry, health, energy, food and agriculture

Summary

Well recognized as an important pillar in chemical technologies, CSET (Chemical Sensing & Enabling Technologies) is regarded as a science domain within all key enabling clusters. Equally important is the innovation potential of the high-tech systems industry in The Netherlands, with a significant number of SMEs and large industries focused on the design, development and application of chemical technologies; strengthening this domain will positively impact the earning capability of the Dutch economy. Therefore, CSET forms an important and key asset in the mission-driven innovation program, addressing the sustainability challenges and the national focus areas as defined in the KIA 2020 - 2023.
In the CSET roadmap 2020 - 2050, the technological challenges related to these “sleuteltechnologieën” are discussed within the framework of the four other innovation themes, yet with a certain degree of specificity and restricted to the overall innovation challenges increasing focus and allowing breakthroughs within the forthcoming decade. This roadmap will allow multi-disciplinary research consortia between industry, (technical) universities, HBOs and TO2 to be formed within the context of the following focus areas:

Energy Transition & Sustainability

- Design and development of robust and universal multi-model sensing technologies for both chemical (molecular) and physical (fluidics) information.
- Improved statistical and data sciences of sensor readouts (digitalization).
- Flow chemistry, design and development of novel flow reactors for µL to multiple L flowrates, with increased understanding of, e.g., mass and heat transport facilitating electrification.
- New materials for (re)design of sensor and enabling technologies.

Agriculture, Water & Food

- Sensitive and selective detection of food quality during processing for improved health and wellbeing and decreasing food waste.
- Sensors for real-time monitoring of critical molecular parameters for sustainable food processing and more efficient food production.
- Membrane and purification technologies with on-line sensing in water security; detection of large variety of compounds ranging from heavy metals to chemical impurities.

Health & Care

- Advances in “Organ-on-Chip” like high throughput screening technologies combined with approaches in on-line detection.
- Improved accuracy and specificity in (hand-held) diagnostics technologies increasing homecare. Including but not restricted to all classical clinical biomarkers, medication.
- 3D printing technologies for the preparation of personalized medication at pharmacy or home.

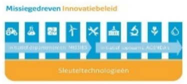
Key Enabling Technologies

- Development of new micro-/nano-fabrication technologies to create functional materials and the chemical modification of materials surfaces.
- Design of new robust (e.g., anti-fouling) materials in novel chemical technologies.
- Multi-modal sensing, advanced reactor design and novel modelling tools, supporting process intensification and allowing reduction of carbon footprint.
- New fundamentals in advanced detection technologies in continuous manufacturing.

Industrial Safety and Process Development

- Novel fixed and mobile (wearable/portable/drone-based) sensors for monitoring specific chemicals of concern in and around a chemical production environment.
- Development of in-/on-line sensors and/or sensing methods (incl. soft sensing) that provide early warning signals for potentially hazardous process deviations or upsets.
- Multi-model analytical technologies with improved chemical, spatial, and temporal resolution for *in situ* measurement of reactants, intermediates, and products and catalyst behavior at different time and length scales.
- Innovative micro-flow reactor technologies for gas-, liquid- and solid-phase chemistries.
- Advances in molecular and process modelling and chemometrics/machine learning for improved process understanding and control.

ChemistryNL

	Energy Transition and Sustainability			Agriculture, water and food	Health and Healthcare	Security	Key Technologies	Societal earning capacity
ChemistryNL Roadmap 	Climate and Energy (IKIA) *in particular Mission C "Industry"*	Circular Economy	Future Mobilitysystems	7 missions	4 missions	8 missions	Key technnology (ST) clusters: ChemTech, AdvMat, DigTech, EngFabTech, LifesciTech, NanoTech, PhotoTech, QanTech	3 tracks
Chemical Sensing & Enabling Technologies							ChemTech, DigTech, EngFabTech, Phototech, LifesciTech, NanoTech	

ChemistryNL

Vision / Goals

It is our mission and ambition to create a national roadmap with high degree of focus on a restricted number or urgently required technological innovations within the context of the national innovation themes. The objectives within this mid- (2030) and long-term (2050) vision document describe new technological solutions on the short term, and fundamental breakthroughs on the longer term. The choices made will allow short-term solutions by e.g. implementation of validated sensor technologies in new application domains. On the longer term, fundamental breakthroughs in the CSET-relevant technologies should create advanced materials for all type of advanced (chemically) functionalized surfaces, fluidic, sensor and reactor technologies. Digitalization, defined as the combination of validated multi-model sensor and data processing tools, is considered essential in order to provide fundamental knowledge of causality in e.g. chemical processes and within all other sciences domains, omics sciences in health care, and customized **continuous** manufacturing in the chemical industry.

Introduction

CSET (Chemical Sensing and Enabling Technologies) is organized within the domain of the chemical sciences, and by their nature are applied among many science areas being essential in clinical diagnostics, food safety, the production of industrial chemicals and throughout the complete R&D value chain in drug discovery. They encompass the technological sciences related to, e.g., fluidics systems (micro flow-reactors, lab-on-the-chip), the fabrication of e.g. chemical functionalized surfaces or materials (3D printing technologies, energy storage) and a wide range of sensor technologies (micro-spectroscopy, diagnostic binding assays). Its importance for the Dutch National Science (NWA) agenda is well described in the routes “Measuring & Detecting” and “Advanced Materials” and referred to in routes such as “Precision Medicine” and “Smart Industry”. The roadmap chemical and enabling technologies strongly relates to the KIA Key technologies. The contribution of CSET to the KIA Key technologies is partly embedded in the multi-year plans (MJPs) MJP 71 *Measuring and detecting technologies* and MJP 72 *Evidence-based sensing*.

Likewise, sensing and enabling technologies are on a National and European level regarded as an important asset within the “Key Enabling Technologies”. The “Nationale Sleuteltechnologieën” are one of the five major pillars of the mission-driven strategy for research in The Netherlands, encompassing nine major technology platforms, all covering a wide range of enabling technologies. The Suschem Strategic Innovation and Research Agenda (SIRA), compiled by the Federation of European Chemical Industry (CEFIC), has been accepted as integral part of the European JTI SPIRE, whereby chemical sensing and enabling technologies (digitalization) will form one of the three pillars for the calls dealing with the “chemical industry transition” within the Horizon Europe framework. Overall, the design and development of advanced fabrication, sensing and enabling technologies are regarded pivotal to create sustainable “continuous customized manufacturing” in the chemical industry, to improve clinical diagnostics and treatment, to secure food and water safety, to develop efficient energy storage and conversion, and will form an integral part of high-tech systems for aerospace, homeland security and intensification of the agricultural sector.
Well recognized as an important pillar in chemical technologies, the chemical sensing & enabling technologies (CSET) is regarded as a science domain within all key enabling clusters. Therefore, the CSET roadmap forms an important and key asset in the mission-driven innovation program, addressing the sustainability challenges and the national focus areas as defined in the KIA 2020 - 2023. The CSET roadmap 2025, the technological challenges related to these “sleuteltechnologieën” are discussed within the framework of the four other innovation themes, yet with a certain degree of specificity and restricted to the overall innovation challenges increasing focus and allowing breakthroughs within the forthcoming decade. This roadmap will allow multi-disciplinary research consortia between industry, (technical) universities, HBOs and TO2 to be formed within the context of the following focus areas:

Energy Transition & Sustainability
With the long-term vision on energy and sustainable “customized continuous manufacturing”, the chemical and high-tech materials industry will have to undergo a fundamental transition from a highly intensified and efficient, to a flexible and tailored portfolio of different products and processes. The quality of feedstock, originating from fossil or biobased materials or even recycled materials, the security in having access to water and energy (electrification) will require advanced materials in membranes, robust chemical inert surfaces of sensors and a multi-modal solution for the detection of an extremely wide range of chemical entities. Connected with these needs are the digital sciences that will make crucial contributions to these challenges.
In this mission, focus will be on:

- Design and development of robust multi-modal (spectroscopy) sensing technologies for both chemical and physical readout, based on advanced surfaces and materials.
- Digitalization of sensing technologies combined with novel chemometric and modelling tools.
- Novel fraction technologies, e.g., 3D printing, chemical modification of surfaces, design and development of novel flow reactors for µL to multiple L flowrates, with increased understanding of, e.g., mass and heat transport allowing electrification.

Agriculture, Water & Food
As the timely harvesting of e.g. corn will reduce the overall waste of food feedstocks, infrared cameras in drones have shown their added value. Likewise, sensors applied for the early detection of food decomposition will lead to a significant reduction of discarded “expired” food. Although some promising and effective applications have been implemented, advanced and more sensitive and selective sensing technologies are required to reduce waste to a minimum. In this mission, focus will be on:

- Sensitive and selective detection of food quality during processing, decreasing food waste.
- Membrane and purification technologies with on-line sensing in water security; monitoring of a large variety of compounds ranging from heavy metals to chemical impurities.

Health & Care

Together with the development of multi-modal sensing technologies, higher sensitivity and increased selectivity is a prerequisite in bringing clinical diagnostic tools to the home environment, allowing diabetes and cancer patients to control their personalized medication and well-being without being hospitalized. The same holds for the water companies and the larger chemical industrial sites, facing ever-increasing demands regarding water quality, and the reduction of small molecular pollutants like catalysts or drug degradation products. General societal challenges related to the enormous amount of micro-plastics and other health-impacting microparticles in the environment can only be addressed successfully by the development of new sensing approaches. In this mission, focus will be on:

- Advances in "Organ-on-Chip" like high-throughput screening technologies combined with approaches in on-line detection.
- Improved accuracy and specificity in (hand-held) diagnostics technologies increasing homecare, including but not restricted to all classical clinical biomarkers and medication.
- 3D printing technologies for the preparation of personalized medication at pharmacy or home.

Industrial Safety and Process Development

Advanced analytics and sensoring, data science, and modelling will play a crucial role in developing new processes and improving the monitoring and control in the (petro)chemical, agro/food, and pharmaceutical industries. Improved and extended sensing in the processing industries will benefit the design of new processes (e.g. by improving chemical understanding) and the efficiency and sustainability of processes at plant-scale, but also their safety aspects. As proposed in this roadmap, developments in key CSET technologies are needed to implement "Factory of the Future" and "Industry 4.0" concepts in practice. In this mission, focus will be on:

- Novel fixed and mobile (wearable/portable/drone-based) sensors for monitoring specific chemicals of concern in and around a chemical production environment, and in-/on-line sensors and/or sensing methods (incl. soft sensing) that provide early warning signals for potentially hazardous process deviations or upsets.
- Multi-model analytical technologies with improved chemical, spatial, and temporal resolution, coupled to advances in molecular, process modelling and chemometrics/machine learning, for the design of new processes and products and the *in situ* measurement of reactants, intermediates, and products and catalyst behavior at different time and length scales.
- Innovative micro-flow reactor technologies for gas-, liquid- and solid-phase chemistries.

Key Enabling Technologies

Micro-/nano-fabrication processes play an ever-increasing role in the design and manufacture of new materials, sensing and processing devices, and other technological developments. Development of such fabrication techniques will continue to integrate and bridge the molecular scale with/to the macroscopic one. At the same time, these technologies bestow materials with increasingly advanced functionalities, such as dynamic and life-like properties, anti-fouling and self-healing properties, and the ability to perform complex operations. Micro-/nano-fabrication technologies pervade all areas of the KIA, and are an essential pillar of the Key Enabling Technologies.

Well-engineered Chemical Sensing and Enabling Technologies and novel instrumentation performing at ultimate length or timescales, are likely to generate advanced know-how of chemical and biochemical (biological) reaction pathways on a (supra)molecular scale, and they will generate crucial knowledge of meso-macroscopic properties of novel (bio)materials that can give us (nano) tools in mimicking for diagnostic sensing of (bio)chemical processes at different timescales. The importance of innovations in chemical sensing and enabling technologies can be regarded a pre-requisite for nearly all other domains of sciences and society as a whole. New sensing techniques allowing multi-modal (both physical and based on chemical principles sensing) real-time monitoring of chemical and biotechnological continuous production processes are needed. The combination with efficient chemometric and big data (AI and ML) methodologies will enable the efficient extraction of pivotal information from the sensing data. In the design of flow- & micro-reactors, lab-on-a-chip devices or (bio)sensors have generated fundamental insight in e.g. single cell processes, while classical analytical technologies such as NMR spectroscopy (Ernst, Nobel prize 1996), and very recently super-resolution fluorescence microscopy (Betzig, Hell & Moerner, Nobel prize 2014) have shown their pivotal importance in the molecular profiling and imaging (structure, heterogeneity) of ever more complex (polymeric, fine- & bio-) chemicals, materials and (bio)processes [2]. The integration of these type of technologies, e.g. mass spectrometry and electron microscopy, are examples of technologies able to simultaneously address the morphology and the chemical composition of complex materials. In biology, label-free sensing technologies are highly required.

- Development of new micro-/nano-fabrication technologies to create functional materials and the chemical modification of materials surfaces.
- Design of new robust (e.g., anti-fouling) materials in novel chemical technologies.
- Multi-modal sensing, advanced reactor design and novel modelling tools, supporting process intensification and allowing reduction of carbon footprint.
- New fundamentals in advanced detection technologies in continuous manufacturing.

It is this council's ambition to address all these technological challenges and create on the short- (2030) and long-term (2050) a path forward in the design, development and implementation of "The technologies of the Future". Our roadmap encompasses the scientific and industrial communities engaged in nanomaterials development, (flow) micro reactors with sensors to monitor (bio)chemical and biological cell systems, (bio)sensors measuring at different time scales and classical state-of-the-art analytical technologies with ultimate chemical or spatial resolution. It anticipates on societal and industrial trends like biomimicking materials, "bringing the lab to the sample", value-added process control (reliability) by multiplexed sensing, and personalized medicine. Meanwhile, it seeks for a clear link with the other "Topsector Chemistry" roadmaps, being well addressed in the National Research Agenda and the European Horizon Europe Program, further improving cross-science synergy, regarded as a key differentiator for the position of the Dutch economy and the sustainability of basic and applied research. Hence, an intensive interaction between academic research in nano-chemical and analytical technologies, industrial R&D organizations and the large number of SMEs marketing novel instruments truly valorizes the "excellences in Dutch research communities" into innovative and novel products. This approach will to a large extent solve the identified "TRL" problem, well-known as the "valley of death", being one of the top priorities in the European Horizon 2020 program. Additionally, in this way options for valorization are created in "non-chemistry" domains such as security and law enforcement, e.g. handheld devices to screen for drugs at crime sites. In relation to nanotechnologies, "nano-safety" will be a generic topic throughout the research and development foreseen in the different tasks and related to the RIVM research and relevant programs addressed within the roadmaps and R&D focus of the ISPT, MinacNed and NanoNextNL organizations.

Key Technologies

The Key (enabling) Technologies defined as the fifth mission, are regarded an integral and an essential toolbox, facilitating solutions for the globally defined societal challenges and enabling the objectives of the National Mission Driven Innovation platforms to be met. Organized in nine “sub-classes”, they cover a wide variety of sciences including chemical, life sciences and logically the recently introduced digital and quantum technologies. While an important pillar in chemical technologies, the Chemical Sensing & Enabling Technologies (CSET) can be considered as an overarching science domain being, to a larger and lesser extent, interlinked with the majority of these eight pillars. This is visualized in Table 1, depicting the interlink, and the impact (number of links with the different key technologies) of classical chemical technologies.

Knowledge on microfluidics, either in micro flow-reactors or as basis for sensors, is of added value in the design of organ-on-the-chip (life sciences) devices and sensitive and specific sensors for food safety require the development of novel (chemically) functionalized surfaces (molecular imprinted polymers). Likewise, cantilevers being an essential part of atomic force microscopy, are of comparable importance for sampling in single cell analysis (nano technologies). Sensors based on comparable principles, yet applied in the chemical industry require more “inert” materials able to withstand hazardous (oxidation, corrosion) conditions, while the high quality manufacturing of enabling technologies, heavily rely on new engineering and fabrication (3D printing) technologies. The widely applied nearby infrared (NIR) sensors form an important class of instrumentation in the photonics and light technologies.

		Technology							
Key Technology Cluster	**Connection to CSET**	*Microfluidics*	*Spectroscopy*	*Separation Techniques*	*Sensors*	*Modelling*	*Data Science*	*Imaging & Morphology Techniques*	*Chemical Element Analysis*
Chemical Technologies	Very strong	x	x	x	x	x	x	x	x
Life Science Technologies	Very strong	x	x	x	x	x	x	x	x
Advanced Materials	Strong		x		x	x	x	x	x
Nanotechnologies	Strong	x	x	x	x			x	x
Engineering and Fabrication Tech.	Strong	x		x	x	x		x	x
Photonics and Light Technologies	Medium		x		x			x	
Digital Technologies	Medium				x		x		
Quantum Technologies	Weak				x				

Table 1: Key technologies and their connection to the CSET roadmap

Although different in application, the challenges for all technologies can be summarized in a set of general nominators. The robustness, accuracy/ precision, standardization, sensitivity, selectivity, dynamic range, speed are some of them and form a set of “application requirements” in the (re)design of future sensing, micro-fluidics and micro/nano fabrication processes.

Micro/nano-fabrication processes play an ever-increasing role in the design and manufacture of new materials, sensing and processing devices, and other technological developments. Development of such fabrication techniques will continue to integrate and bridge the molecular scale with/to the macroscopic one. At the same time, these technologies bestow materials with increasingly advanced functionalities, such as dynamic and life-like properties, anti-fouling and self-healing properties, and the ability to perform complex operations. Micro/nano-fabrication technologies pervade all areas of the KIA, and are an essential pillar of the Key Enabling Technologies.

Well-engineered Chemical Sensing and Enabling Technologies and novel instrumentation performing at ultimate length or timescales, are likely to generate advanced know-how of chemical and biochemical (biological) reaction pathways on a (supra)molecular scale, and they will generate crucial knowledge of meso-macroscopic properties of novel (bio)materials that can give us (nano) tools in mimicking for diagnostic sensing of (bio)chemical processes at different timescales. The importance of innovations in chemical sensing and enabling technologies can be regarded a pre-requisite for nearly all other domains of sciences and societal as a whole.

New sensing techniques allowing multi-modal (both physical and based on chemical principles sensing) real-time monitoring of chemical and biotechnological continuous production processes are pivotal for the envisioned age of “customized continuous manufacturing” of base chemical, circular materials and personalized combination drug treatment (delivery of personalized drug formulation during chemocures).

While classical technologies such as NMR spectroscopy (Ernst, Nobel prize 1996), and very recently super-resolution fluorescence microscopy (Betzig, Hell & Moerner, Nobel prize 2014) have shown their importance in the molecular profiling and imaging (structure, heterogeneity) of ever more complex samples [2], the obtained information can be regarded still limited. The integration of these type of technologies and the fusion of their data is a highly needed perquisite in order to simultaneously address the morphology and the chemical composition of complex materials. Multi-modal and integrated sensing and enabling technologies are defined as critical in the CSET roadmap!

Technological challenges

As mentioned above all challenges of particular importance for specifically the sensing and enabling technologies are related new approaches in the fundamentals of sensing technologies, new measurement principles, e.g., creating high selective detectors. Improved robustness can be can be reached by the design and application of new materials, while pricing and miniaturization (standardization) are relaying on improved fabrication processes. In short, the technological challenges are in general both fundamental by nature, still in the lower TRL level stages 2-6, envisioned to serve the long term planned innovations. Not aiming to be comprehensive, the CSET roadmap focusses on the following technological challenges;

- Development of new micro/nano-fabrication technologies to create functional materials and the chemical modification of materials surfaces.
- Design of new robust (e.g., anti-fouling) materials in novel chemical technologies.
- Multi-modal sensing, integration of classical high-resolution technologies, e.g. AFM-Raman, EM-MS.
- Advanced reactor design and novel modelling tools, supporting process intensification and allowing reduction of carbon footprint.
- New fundamentals in advanced detection technologies in continuous manufacturing.

Cases

Multi-modality sensing (for in-situ analysis of chemical conversion processes).
Task
The fundamental principles of chemical conversions, and the mechanisms underlaying the well described heterogeneous- or bio-catalytic processes are still considered incomplete, newer approaches such as photo and electrochemical-catalysis will need novel multi-modal approaches to correlate reaction mechanisms, kinetics and physical parameters (quantum yields in photo (liquid) in catalysis. Here multi-modal technologies could combine information of materials morphology and molecular identification, or combined micro- or milli second reaction kinetics analysis combined with stereoselective detection. Central in this task, is the technological integration of technologies, simultaneously with the fusion of data increasing high density information, compared to the currently “single data point” analysis of dynamic processes.

Goals

Goal	Year	TRL
New chemometric tools, combined with fusion and analysis approaches for data originating for different sensing technologies, with improved information density	2030	4-8
Integration of measurement of classical detection and sensing technologies	2040	5-9
Integration of data from physical and molecular sensing technologies allowing the causality analysis of dynamic processes	2050	2-6
Cross-validate new multi-modal detection technologies to other science domains, mechanistic research of dynamic processes in cellular systems	2050	5-9

Challenges and Route

The most ideal approach to tackle these problems, by creating multi-disciplinary research consortia, e.g., having a solid background in chemistry, catalysis, analytical chemistry and instrument engineering. Likewise, to support personalized drug treatment linking the speed and concentration dependent administration of multi drugs with the continuous monitoring of evident biomarkers, or the concentration of the drugs in-vivo, requires, pharmacists, medics and analytical chemist together. From an technological perspective, the engineering of the new integrated “multi-modal” technologies requires knowledge on instrument engineering, not per definition a strongly develop competence at universities. Collaboration between instrument manufactures and academia, TO2 and Universities of Applied Sciences is a pre-requisite!

Possible Research

a. Integration of physical and chemical sensing technologies, for example dynamic light scattering, viscosity and UV/VIS in polymer analysis.

b. Multi-modal spectroscopic imaging (fluorescence and IR)
c. Combining morphology (EM) and spectroscopic or spectrometric technologies.
d. Data fusion and chemometric tools in the digitalization and data fusion, e.g., NMR and MS imaging technologies.

Development of new micro/nano-fabrication technologies to create functional materials and the chemical modification of materials surfaces.

Task

State-of-the-art sensor technologies based on molecule-molecule interaction frequently suffer form a-specificity, e.g., as is the case in antibody – small interactions in ELISA type principles. Measurements of "heat of interaction", or change of angle of light incidence (SPR) still often allow very sensitive measurements. Central in this task is the (re)design of sensors based on novel principles, e.g., molecular kinetics not leading to loss of sensitivity. Integration of various sensors in one array would facilitate multi-modal detection. Despite "molecular imprinted polymers" have shown their value, still improved fabrication methodologies are needed. Central, in this task is the development of new functional surfaces supporting new measurement principles.

Goals

Goal	Year	TRL
Redesign and improvement of selectivity of existing sensor technologies	2030	6-9
Proof-of-Concept in new measurement principles based on advanced functionalized (sensor) surfaces. Application of new materials with improved physical properties (conductivity, stability)	2040	3-6
New improved (low-cost) fabrication processes for functionalized materials and surface for new sensor technologies, fluidics-based production processes	2050	2-6

Challenges and route

The challenges related to this task are to a large extent related to the availability of new functionalized materials and/or material surfaces. In addition, standardization and validation of new (nano) fabrication technologies is regarded essential. As for all other research within this roadmap, multi-disciplinary teams address the challenges are the most effective approach.

Possible research

e. 3D-printing technologies for the fabrication of inert materials.
f. New chemical processes for the functionalization of surfaces.
g. Fabrication processes for array detection, incorporating different sensor technologies
h. Combining morphology (EM) and spectroscopic or spectrometric technologies.

Design of new robust (e.g., anti-fouling) materials in novel chemical technologies.

Task

In-line with new measurement principles (previous task) and the introduction of new functionalized surfaces and the fabrication thereof, robustness of sensor technologies remains an essential property, especially when applied in industrial production processes. The future sensing technologies are expected not to be prone to signal instability due to fouling, signal drifting due to corrosion of the sensor material or even limited live time linked to frequent recalibration. The robustness as such is there for highly linked to fabrication (high quality standards), and the availability of new materials. Yet, it tends to go beyond these as aspects and therefore deserves special attention.

Goals

Goal	Year	TRL
Continue design and optimization of currently developed new materials, validation of these current approaches in industrial setting	2030	4-9
Development of multi-array sensor technologies to compensate for "natural drift" of sensing technologies.	2040	4-6
Continued research of new materials (e.g., diamond based) able to handle "hazardous conditions"	2050	2-6

Challenges and Route

Many challenges are related to the availability of anti-corrosive materials which allow efficient light transmission and sensitive detection. Also, it should have properties such that high-throughput production is possible.

Possible Research

a. Translation of anti-fouling properties of biomedical application or anti-corrosive coatings applied in off-shore application to sensor technologies.
b. Novel chemometric and statistically approaches in compensating sensor fluctuations.
c. Cross validation of e.g. quartz sensor probes from chemical industrial application to biomedical methodologies.

2 Energy transition and sustainability

2.1 Climate and energy

Climate and Energy refers to a reduction of greenhouse gases by 49% in 2030 compared to 1990 and to almost zero in 2050. Important aspects are the multitude of sustainable energy sources (wind, solar, biomass, etc.), the need to convert energy from these sources into a form that people can use in their lives (electricity, liquid, gas, etc.), storage of energy when supply is bigger than demand, and release in case of the reverse scenario. Given the cost of sustainable energy, efficiency is vital for its introduction. In general the generation of renewable energy requires improved materials and systems. Due to the scale that is needed for this transition, the challenge will be to scale-up existing technologies to very large scale in the next 10 years and come up with new, improved technologies for the long term. Electrification, re-use of waste streams and Carbon Capture and Usage (CCU) have a need for new materials and processes.

In this roadmap, we discuss the creation of materials, processes, devices and systems in order to:

- Store 'sustainable electrons' in cheap, stationary batteries with a high conversion efficiency. Affordable and available raw materials are needed when scaling-up to the GW range.
- Convert 'sustainable electrons' into chemical bonds to obtain a gaseous (e.g. hydrogen) or liquid (e.g. methanol or ammonia) fuel that can be stored more easily.
- Improve the conversion efficiency of photovoltaics and thermoelectric conversion devices.
- Develop heat pumps for cooling and/or heating in the urban environment.
- Develop heat storage materials (phase change/hydration) in which the nanostructure (essential for fast kinetics) remains intact. Nano-structured thermal insulation materials for houses.

Technological innovations are needed in the fields of:

- Novel characterization technologies; e.g. for studying (electro-)catalytic processes *in operando*.
- Novel tools and methodologies for R&D, for example to understand charge transfer processes in complex, multicomponent systems.
- Investigate nanoscale electrochemistry and nanofluidics.
- Novel materials & processes; e.g. for the electrochemical conversion of CO_2 and H_2O into hydrogen and hydrocarbons, for third generation solar cells, and the electrochemical conversion of N_2 to NH_3.
- Novel fabrication technologies, for nanostructured dimensions; e.g. for the controlled fabrication of large scale (>>m^2) nanostructured surfaces with high-performance photovoltaic or catalytic functionalities (and combinations thereof), e.g. for the development of hybrid organic/inorganic membranes.

Cases

Electrochemical reduction of CO_2 with minimum over-potential

Task

In the coming decades we will see a transition from CO_2 as a pollutant to CO_2 as a resource. CO_2 capture will become common practice and its conversion to fuel a necessity. Fuels have the advantage that they can be stored for long times to bridge seasonal inbalance. Hydrocarbons are easily integrated in the present fuel infrastructure and can be directly used as a resource in the chemical industry.

In order to deal with the enormous seasonal mismatch in energy use and production, it is vital that we connect the fuel infrastructure to the electricity grid. Thus, electrochemical conversion processes will become key in a sustainable society. These processes, however, suffer from low conversion efficiencies, poor selectivity, a high demand for precious metals and a poor resilience against fluctuating process conditions. To solve this a revolutionary breakthrough in the field of electrochemistry is required.

Goals

Goal	Year	TRL
Computational methods to reliably determine the nature of the intermediate state during the reduction of CO_2 on complex nanostructured surfaces, taking the electrolyte into account	2030	4
New *operando* methods covering all aspects of electrochemistry	2040	6
Devices combining short-term storage and electrolysis at local scale	2030	8
Solar fuels, including water splitting	2040	6

Challenges and Route

To address this task successfully collaboration is required of the electro-catalysis community with scientists specialized in nanotechnology and classical catalysis, and the *operando* surface characterization communities. The electro-catalysis community has so far focused its research on elemental electrodes and phenomenological studies on the processes involved in electro-catalysis. Computational studies have shown that elemental electrodes will not be able to catalyse oxidation/reduction reactions at sufficiently low over-potential. Stepped, non-elemental surfaces are needed to provide intermediate states at low enough energy. This opens a new area of application for the nano-community to develop tools to design and develop manufacturing methods to produce large area nano-structured surfaces for electro-catalytic applications. Besides nano-structuring for tuning of electrode selectivity and stability, this can also aid in optimization of transport phenomena and manipulation of gas bubble dynamics on electrode surfaces. The nature of such surfaces cannot be established from computational methods alone. Therefore, in electro-catalysis there is a great need to develop methods to investigate the charge transfer processes on an atomic scale in *operando* conditions.

Possible research

- Computational methods to reliably determine the nature of the intermediate state during the reduction of CO_2 on complex nanostructured surfaces, taking the electrolyte into account.
- New *operando* methods covering all aspects of electrochemistry.
- Efficient (bio)chemical sequestration of CO_2 .
- Devices combining electrochemical storage and electrolysis at local scale.
- Nanostructured alternatives for lithium-based storage systems.
- Solar fuels, including water splitting.
- Energy production and storage at point of use.

Towards a third generation solar cell

Task

Solar energy is the largest renewable energy source on the earth. The sun delivers around 2000 times more energy than the current global primary energy consumption (550 EJ). Direct conversion of solar radiation into electrical energy using solar cells has proved to be a viable option for electricity generation. The challenges for an accelerated large-scale implementation of solar cells are both cost reduction and efficiency enhancement of solar cell technologies. Reduction of costs can be realized by replacing expensive bulk semiconductors (e.g. silicon) by photovoltaic materials that can be deposited by cheap (wet-chemical) techniques. The efficiency of a conventional solar cell is limited mainly by the fact that 1) infrared photons with energy below the band gap of the photovoltaic material are not absorbed, and 2) the energy of absorbed photons in excess of the band gap is lost as heat. The third generation solar cells to be developed should be based on cheap materials and the above-mentioned limitations to the efficiency must be overcome (e.g. tandem solar cells)

Goals

Goal	**Year**	**TRL**
Development of cheap photovoltaic materials with optimum optical and electronic properties	2030	6
Efficient up- and down conversion technology implemented	2030	6
Improved architectures of nano-materials with optimized device performance	2040	8

Challenges and Route

Cheap photovoltaic materials need to be further developed. Examples of materials include organic (molecular) materials, colloidal semiconductor nanocrystals (quantum dots, nanorods and nanosheets), and perovskites. For large-scale application, it is essential that these materials do not rely on critical elements. Moreover, a rational design approach will be needed to develop processes that combine large-scale production with the nanoscale precision and long lifetime required.
The optical and electronic properties of these materials can be tuned by variation of both chemical composition and nanostructure.
It is important to develop materials in which infrared photons can be upconverted to shorter wavelength photons; e.g. by fusion of low energy triplet excitons into higher energy singlet excitons that emit light at shorter wavelength. Spectral downconversion of photons with energy exceeding twice the material band gap is another option to enhance the solar cell efficiency. To this end materials for quantum-cutting need to be developed.
A very promising novel approach to boost the current delivered by a solar cell involves excitation of two or more electrons by the absorption of a single energetic photon. To realize the above, architectures of (composite) nanostructured materials need to be developed and their performance in real devices optimized.

New heat pump technology

Task

Nowadays a large percentage of the total energy consumption is coming from heating and cooling technology. The state of the art technology are based on compressors using refrigerants that have a large Global Warming Potential and have a negative impact on the ozone layer. In the Kigali amendment to the Montreal protocol the phase out of these gases is planned. Alternative gases are flammable hydrocarbons or carbon dioxide. The latter one can only be applied at very high pressure which drives down the efficiency and increases the costs. Therefore new technology needs to be developed.

Goals

Goal	Year	TRL
New solid state magneto-caloric materials with improved performance	2030	6
Improved thermo-acoustic technology	2030	8
Heat-pump technology with zero GWP and no ozone depleting gasses	2040	8

Challenges and Route

One route to complete this task is the development of a thermo-acoustic device or use of solid state materials. The latter one uses the magneto-caloric effect of soft magnetic materials. Present materials are made of earth abundant and affordable raw materials, such as Mn, Fe, P and Silicon. The performance is approaching commercial viability, but further improvement in material properties are crucial for replacement of the existing compressor technology. In the heat pump the magneto-caloric energy is transported by a heat transfer fluid. In that case the use of gases phased out faster.
Heat pumps can also be used for heating of residential areas building heat-nets. As cold source for the heat-pump the constant temperature of a drinking water company can be used.
In the industry low temperature waste heat can upgraded to a temperature where it can be used for heating or distillation.

Grid storage and hydrogen production

Task

Currently, large wind-parks in the North-Sea and large solar farms on land are realized. This means that the inbalance in the production of electricity will increase dramatically. Therefore large scale battery systems are required for short term buffering of this inbalance. In the summer period large excess of renewable energy is produced at times when the consumption is low. This large excess can be converted by electrolysis of water into hydrogen. The hydrogen can be stored in salt caverns and be stored for times when it is needed.

Goals

Goal	Year	TRL
To develop efficient technology for hydrogen production and storage.	2030	8
To develop large scale battery systems with improved materials for short term storage of excess renewable energy.	2030	8
Installation of infra-structure for energy storage and transport of renewable energy.	2040	8

Challenges and Route

For this task improved battery materials are required. Improved or next generation Li-ion batteries, Sodium-sulphur batteries, Redox flow technology or Ni-Fe battery materials. The latter has a high potential because this battery becomes an electrolyser when overcharged. That means that from a system perspective less power electronics are needed and this could lead to lower capital than a combination of a battery and an electrolyser. The Ni-Fe technology is also able to switch instantaneously from charging to discharging when power is needed to stabilize the net frequency. For an electrolyser this can only be done by a solid state electrolyser or a PEM electrolyser. The solid state electrolyser requires improved materials and electrolytes, whereas for the PEM electrolyser (Pt and Iridium-oxide) new materials are needed to make large scale use possible.

2.3 Circular economy

In an attempt to reduce waste and handle the criticality in raw materials, the circular economy is seen as a valuable alternative in manufacturing. Despite the fact that in some areas (agriculture, constructing, materials industry) good results were obtained e.g. for polyester materials, the developments in chemical industry (with a clear link to food, pharma and materials) have been lacking behind. Thus, a “cradle to grave” approach is more advised for chemical products themselves which provides environmental health & safety (EH&S) compliance and tracking inventory across the whole supply chain from manufacture to disposal. Companies like BASF see such approach as holistic when involving the entire value chain and point here at “traceability” of all impacts (BASF’s Sustainability, Eco-Efficiency and Traceability (SET) Initiative in Schoener et al., Int. J. Food System Dynamics, 2012, 119-131). Green Chemistry is often said to be a 'cradle to grave' approach (Ed Marshall, Imperial College, http://www.ch.ic.ac.uk/marshall/4I10).
In line with the search for alternatives, the EU is committed to development of a state-of-the-art industrial infrastructure focused on innovative and specialty (consumer and industrial) products, together with addressing the so-called TLR 4-6 gap, referred to as the “Death Valley”. Translated to “the chemical environment”, the EU Horizon 2020 programm and it’s successor Horizon Europe embrace a number of “Key Enabling Technologies”, KETs, like nanotechnologies (*Research in this area will lead to new products and services developed by the industry, capable of enhancing human health while conserving resources and protecting the environment*), and advanced manufacturing and processing (*The aim is to increase the competitiveness and energy efficiency of the construction sector, to increase sustainability of production processes and make the process industry more resource- and energy efficient*). An application area, asking for major technology breakthrough, is the so-called Bio-based chemistry. A considerable part of the Horizon programs is directed to this theme, being also embedded in the TopSector roadmap “making the molecules of the future”.
A promising technological trend that has been developing, and which is of added value for the bio-based industry, is (micro) flow (bio) chemistry. Over the last decade significant academic research has been performed, some small-scale systems are commercially available, and the potential to further improve resource (raw materials) efficiency, process reliability have been demonstrated. Moreover, increased attention in microreactor (gas, liquid or solid phase chemistry) sciences are carried out on lab scale, either with the hope of generating enough material that scale up will not be needed, or with the hope that the information gathered from the lab experiments can be better translated to continuous large-scale processes. For the translation of small to large scale flow chemistry, process monitoring and control technologies (sensing) and general analytical technologies to characterize the feed-stock, the product and the catalyst *in operando* at ultimate length and time scales, is crucial. Overall, it is anticipated that this trend will continue, and we see several immediate and long-term ambitions. We have a chemical industry that is able to develop clean processes with minimal waste under a competitive time pressure, on a small lab scale, such that these clean processes are easily scaled up to reliable robust plants. The reliability is especially relevant for varying feed stocks, which is destined to become more prominent as biomass and other sustainable sources of chemicals come to the forefront.

This task discusses the required innovations in order to

- Improve resource (raw materials) efficiency, e.g. high selective processing and recycling of non-reacted material or development of devices allowing novel chemistry (e.g. photochemistry).
- Promptly design and development of “first time right” (having fundamental understanding of processes on molecular level) innovative (larger scale) chemical production processes at larger scale, e.g. feasibility studies on feedstock variability for novel (bio) chemical processes like catalysed depolymerisation at micro-scale leading to “process mapping”.
- Realize highly reliable (bio) industrial processes leading to ultimate quality and reduced “out of specification”, e.g. tailored process monitoring of dairy (colloidal systems) production.

Technological innovations are needed in the fields of:

- Novel micro- and large scale “flow” (gas, liquid and solid) reactors; e.g. for the production of nano-particle drug delivery systems, dairy products, mimicking biochemical processes and (catalyzed) cracking (e.g. pyrolysis) of emerging bio- feed stocks.
- State-of-the-art analytical technologies with ultimate chemical, spatial and temporal resolution for the (macro) molecular characterization (structure) of (bio)catalysts, emulsions or novel drug delivery technologies for complex (bio)pharmaceuticals.
- Novel tools and methodologies to create fundamental insight the body response to compounds, materials and devices; e.g. by characterizing the bio-functionality of surfaces and interfaces, and by realizing human disease and organ model systems on a chip.
- Novel on-, in- and at-line detection technologies (sensor systems) for real time detection of catalyst and other chemicals, at ultimate length scale.
- Advanced chemometric, statistical and process modelling technologies for the ultimate control of industrial processes.
- Novel analytical technologies for detailed feed stock characterization, addressing envisioned need in handling larger varieties. (sensors and other on-, at- or in-line detection); base chemicals, raw milk, biomass, water, catalysts.

Cases

Recycling of (raw) materials
Task
An emerging approach to reduce the “inefficient use” of raw materials, limit the waste stream or even use waste (CO_2 in gas phase chemistry after pyrolysis) as energy source or material resource, “flow chemistry” and more generally process intensification have already proven as alternative of today’s conventional processing.

Goals

Goal	**Year**	**TRL**
High efficient and sustainable (bio) catalyst embedded in flow-reactors.	2020	4
Proof of concept for low energy, resource efficient and waste less chemical flow process, including up-stream and downstream processing, towards final product.	2030	5-9
Operational “Factory of the Future” on the basis of efficient use of energy and resources, without waste streams lacking economic value.	2040	4-9

Challenges and Route
The design and use of chemical flow reactors with an ultimate efficiency in resource efficiency, without any waste at an industrial scale is the main challenge.
To complete this task progress is required both scientifically, industrially and societally. Scientifically, new and intensified chemical routes and catalysts are to be developed to be open for the coming diversity of resources and propose end-to-end process designs with fully closed cycles. Enable to make new products and introduce new platform chemicals. Explore new processing, small-scale continuous (micro/milli-flow with nano-functionalities and -sensing), tailored solvents and alternative activation (photo-VIS, electrochemical, plasma, MW, US). In industry existing resources can be used more efficiently and prepared step by step to integrate new resources (biomass, CO2) in the existing Verbund production; close material and energy cycles within the integrated chemical production; switch partly from batch to continuous. For these innovations to be successful the societal image of chemistry has to be changed from one-way resource use/waste generation to sustainable, green enabler with well-balanced resource mix comprising renewables and most efficiently used fossil sources. Change from problem generator to problem solver. Keep and strengthen jobs within Europe. Prepare education for technology convergence.

Possible Topics
- High selective processing and recycling of non-reacted material.
- New and increasingly diverse resource streams: biomass economy, CO_2 as building block, alternative N-fixation, H_2 from photovoltaic water splitting, and artificial photosynthesis.
- New reaction pathways: direct (‘dream’) reactions using largely available, cheap starting materials and making former intermediate steps superfluous.
- Shrunk reaction pathways: all-continuous multi-step and telescoped syntheses (cascades), eliminating intermediate separation.
- Integrated process pathways: further improving the value added chains within a ChemPark and designing new processes with that vision.
- More efficient use of catalyst and recycling hereof and assorted components (e.g. ligands).
- Reduction of organic solvent load (carbon footprint), finally down to zero (solvent-less).
- Reliable (quality) nano-micro flow processes for the production of “nano-devices” serving as drug delivery systems.

3 Agriculture, water and food

In order to provide the future world population with sufficient, and healthy food products, and safe water, the way that agriculture and water production are currently carried out need to be rethought in such a way that the impact on our planet is reduced and ideally minimized, therewith adding to resilience. For example, the food industry is responsible for 10% of the greenhouse gases produced in The Netherlands, and this can be reduced considerably using advanced sensing techniques based on nanotechnology. Besides, there is an imminent climate effect in the choices made for ingredients (e.g. animal based proteins have ~ 10 times higher impact on our climate compared to their plant-based counterparts). Furthermore, water quality is becoming more and more of a worry due to increased prevalence of e.g. components related to medicine usage. In order to mitigate this, advanced nanofiltration techniques need to be developed.
Within this roadmap, we target (food)materials, processes, devices and systems that make food and water production intrinsically more sustainable, reliable, and safe. Points of attention are:

- Advanced sensing technology to allow precision nutrient dosing to agricultural crops either in the field, green houses, vertical farms, etc.
- Sensors for the real-time monitoring of critical molecular parameters. The sensors will enable closed-loop control for sustainable food production and processing in different food chains.
- Smart controlled delivery devices that minimise e.g. herbicide usage.
- Temperature sensors that allow food production systems to enhance food quality, and reduce food waste.
- High-tech separation devices that facilitate production of effective raw materials (e.g. to facilitate the protein transition).
- Same, but for warranting water quality (and effective removal of e.g. pharmaceutical residues).
- Devices that allow high-throughput screening of ingredient functionality to speed up food product design.
- Comparable devices as organs-on-chips but now specifically to test the effect of nutrients on organs. Ultimately these two last points will be the stepping stone toward personalised nutrition directed at creating health effects.

In all attention points, the use of nano/microtechnology is essential because the determining factors act on nano- and micrometer scale, which can uniquely be assessed by these technologies.
A special point related to the time that we live in is zoonotic diseases that are very much linked to food, and for which currently various techniques are under development.

Cases

Water purification and safety
Task
In order to make the Dutch water systems robust (management of scarcity and abundance), and safe (free of contaminants), advanced monitoring and separation methods are needed. Specifically the prevalence of pharmaceutical residues is become more and more of an issue, since these components can be hormonal in nature (birth control), and thus affect wild life in our rivers, and also humans if present in our drinking water. Furthermore, the presence of antibiotics will impact water purification plants as we know them, since the micro-organisms that are applied are affected by it, and also some species may become resistant to antibiotics leading to potential health threats.

Goals

Goal	Year	TRL
Advanced (membrane) separation, and hybrid technologies that allow specific removal of medical components.	2020	3
Separation devices with uniform pores in the (sub-)nanometer range, and anti-fouling properties that allow them to operate in tandem with microbial water treatment methods.	2030	7
Innovative separation concepts directed toward removal / destruction of antibiotics/antimicrobial components to thus reduce resistance issues.	2030	6
Integrated water treatment systems directed to affordable and inherently safe potable water for all.	2040	8

Challenges and Route
It is of the greatest importance to develop advanced separation technologies that target these health-threatening components. In the field of membranes, various options are available, but unfortunately the pore sizes that they have are not well enough defined, and that is what would need to be done if classic filtration is applied. Besides these membranes can be functionalized to make them more specific for a target components, and possibly, they can be used in

combination with other driving forces as currently used (e.g. an electric field instead of the classic option pressure). In this way the separation technology can be made specific, and efficient; and for that structure formation at the nanometer scale would need to be carried out.

Microfluidic devices and sensors for food production and monitoring

Task

Chemical and biochemical research increasingly exploit the use of microfluidic devices and sensors for the detection and synthesis of compounds and for tailoring formulations to maximize the effectivity of the compounds. For example, in food production the quality of soil and water is continuously monitored to optimize production on the land, allowing for precise harvesting transport and storage strategies, that in turn lead to optimal food security and safety. In post-harvest processing, sensors with molecular precision will enable the real-time monitoring of critical molecular parameters. The real-time biochemical data will allow for closed-loop control in order to enable sustainable food processing in different food chains. The developed technologies will be a cost-effective means to increase product quality levels, reduce waste, reduce energy, and increase safety control of existing and new production methods. Micro-technologies allow for the synthesis of small amounts of high-value specialty products and allow controlled structure formation, relevant for food. Such technologies will enable the seamless upscaling from research to production ('scalable flow chemistry'), which will be very helpful for innovations in nutrition. Besides, microfluidic technology and sensing is of great relevance for testing technical component functionality. For example, to make the protein transition possible and allowing animal-based proteins to be replaced by their plant-based counterparts (one of the primary sustainability targets of the Dutch government), it is essential that functionality of these components can be tested on small scale, to allow for fast product formulation and development. Another illustrative example relevant to both food and medicine is the use of sensors on individual products to monitor the quality of the content; this would take us into a new realm in which the good to be used until date will be replaced by an indicator that directly indicates whether a product is safe to use, and thus greatly prevents waste.

Furthermore, there is a clear link with the previously addressed organ-on-a-chip applications, that may be considered as a next step to link the properties of a food or medicine to effects created in the body. As such these devices will allow us to either eat, or keep ourselves healthy at a level that is currently unheard of. Application examples are miniaturized (multiphase) flow systems for enzymatic cascade reactions, and the development of encapsulates for targeted compound delivery with sustained activity ('formulation').

Goals

Goal	Year	TRL
Food testing is done in centralized laboratories.	2020	9
Highly efficient and sustainable food production lines make use of advanced sensing using micro- and nanotechnology, thus creating safe and healthy food, while minimizing food waste, waste water, and energy consumption. Sensors will first be used at-line (taking individual samples) and thereafter on-line (continuous sampling and measurement).	2025	at-line: 9 on-line: 6
Food products designed based on proven ingredient functionality, making flexible use of starting materials possible in a way that complies with circular economy principles.	2030	7
Personalized food products and additives directed toward improving individuals' health based on organ-on-a-chip analysis. [personalized eat yourself healthy strategies]	2040	5
Integrated food concepts that can be prepared on demand, thus adding healthy years to peoples' lives, and reducing dependency on health care.	2040	7

Challenges and Route

The development of the previously mentioned microfluidic devices requires a crossover between partners in micro/nano-technology, chemical and food synthesis, and biomedical sciences, with a key role for innovative high-tech SMEs. In The Netherlands many micro/nano and biotech SMEs have emerged, backed by world-renowned research groups at universities/institutes. Scientifically, microfluidic technologies are to be developed for the synthesis of new formulation concepts (e.g. encapsulates). Industrially, the added value of food should be improved and the food products are preferably personalized. A positive image of food in society can be achieved by focussing on sustainable and environmentally friendly food products, such as plant-based proteins, fermentation-based production, meat alternatives, and allergen-free products. Therefore the development of sustainable food production processes with intrinsic health benefits for consumers is key.

Sensors for agriculture

Photonic sensors, such as optical spectrometers, that convert chemical and physical quantities into readable signals, are becoming more widespread for metrology and security applications. Increasing health awareness of citizens in Europe has led to an expanding demand for sensorial information: people want to know what they eat and what they drink, what air they breathe, if their water is clean and their housing is not detrimental to their health, whether their heating operates efficiently and their car does not produce too much pollution, whether the public places they enter are safe, etc. There is an increasing role for sensing methods with important social themes. The instant availability of the compositions of materials and substances is a key factor for corrective and improvement actions.

In industrial society the contamination of our environment is becoming an increasing concern. An example is waste, another is food safety. Human and animal health worldwide is increasingly threatened by potential epidemics caused by existing, new and emerging infectious diseases (including from antimicrobial-resistant pathogens), placing a burden on health and veterinary systems, reducing consumer confidence in food, and negatively affecting trade, food chain sustainability and food security. The increasing incidence and more rapid spread of such diseases are facilitated by modern demographic, environmental, technological and societal conditions. Many of the infections are zoonoses, necessitating an integrated, cross-border, "one health" approach to research and public health measures in the human and veterinary field, including the food chain. The European *RASFF* (The Rapid Alert System for Food and Feed) program[1] is an example of a program that addressed these hazards, for which the spectroscopic techniques are highly relevant. Figure 1 shows the number of hazard notifications in 2019.

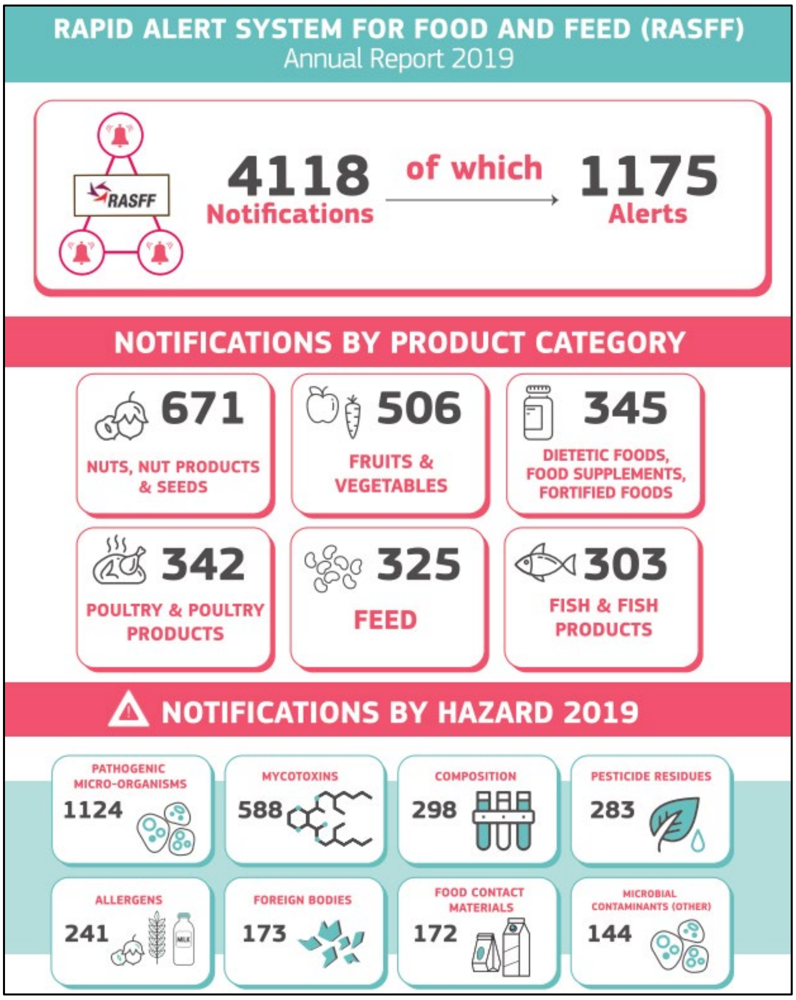


Figure 1: The number of hazard notifications in 2019 of the EU RASFF (The Rapid Alert System for Food and Feed) program[1].

Many corrective programs use spectrometry (optical spectroscopy and mass spectroscopy) as a method to diagnose and monitor the critical elements in the (bio)chemical compositions of water, air, soil, biological tissues, packaging and waste. Target areas are animal health monitoring, food, feed & beverage safety (microbial contamination management, pesticide, agrochemical, veterinary drugs; air, water and soil contaminants). Other application are meat processing, milk analysis, crop management (chlorophyll, water, nutrition).

Microbial contamination management is a crucial task in the food industry. Undesirable microbial spoilage in a modern food processing plant poses a risk to consumers' health, causing severe economic losses to the manufacturers and

[1] See European Commission http://ec.europa.eu/food/safety/rasff/index_en.htm,.

retailers, contributing to wastage of food and a concern to the world's food supply, see Figure 2. The main goal of the food quality management is to reduce the time interval between the filling and the detection of a microorganism before release, from several days, to minutes or, at most, hours[1]. Spectroscopy is an ideal candidate technology for this application because sample preparation is minimal and results are available rapidly (seconds to minutes).

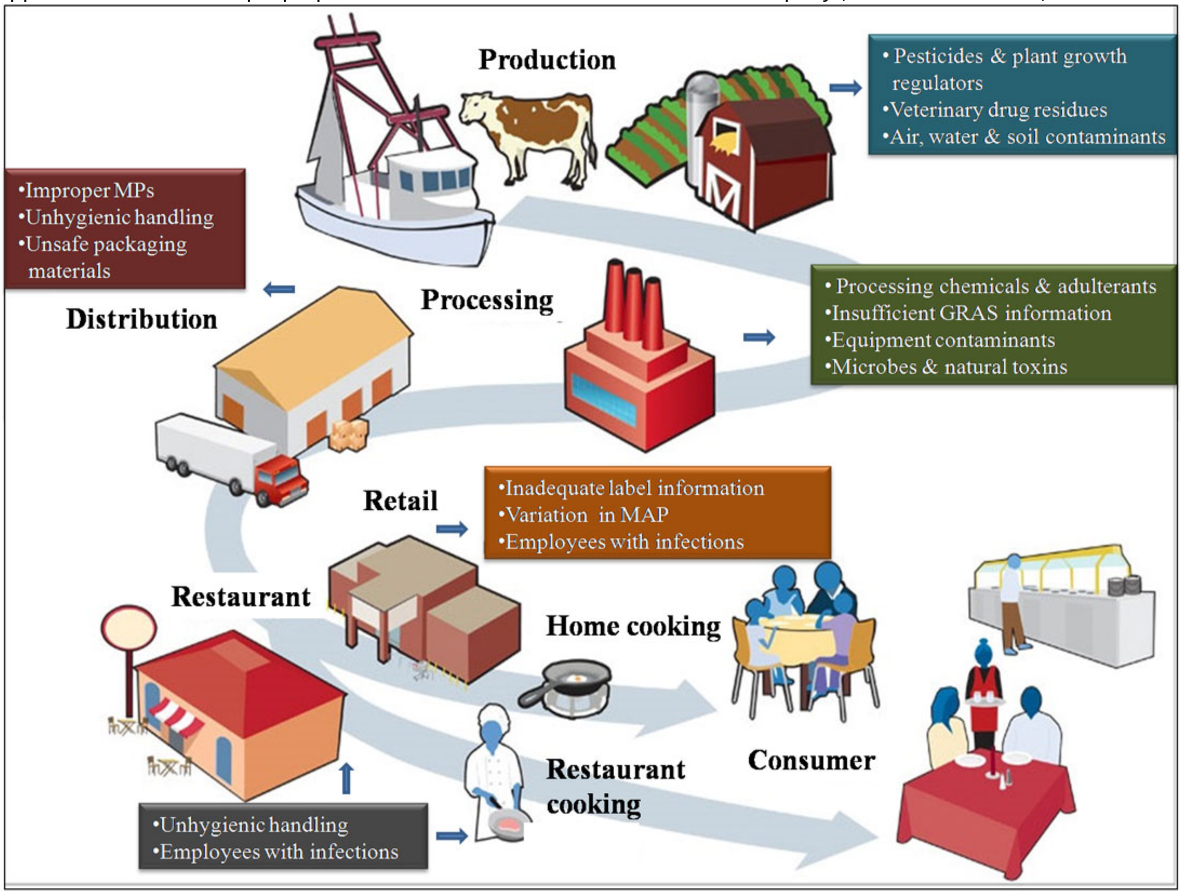


Figure 2: Potential sources of contamination in the consumable food. MPs: Manufacturing practices, GRAS: Generally Recognized As Safe, MAP: Modified Atmosphere Packaging. (Image: CKMNT; adapted from Centres for Disease Control and Prevention (CDC), USA).

The food diagnostic market for the detection of pathogens is expected to grow towards a total market size of $10 bn by 2020. The market is fragmented and players include 3M Company, Thermo Fisher Scientific, Neogen Corporation and bioMerieux. These companies are rapidly adapting their products to sustain their competitive advantage[2]. Competing technologies used for pathogen detection include other biosensors, such as electrochemical biosensors, piezoelectric biosensors and thermal biosensors.

Task

Spectral analysis is a versatile and powerful method to diagnose and monitor food, feed, water, air, soil, biological tissues, packaging and waste. To date there is no good solution for the new challenges in spectroscopy requiring compact and robust devices which can be produced at high volume and low cost.

In industrial society the contamination of our environment is becoming an increasing concern. But also food and feed security and safety, the sustainability of food production, processing and consumption in face of a growing world food demand have become major challenges. Current technology does not provide a solution.

[1] Adley C.C., "Past, Present and Future of Sensors in Food production", 2014.

[2] Markets and Markets, "Food Diagnostics Systems Market", 2014.

Goals

Goal	Year	TRL
Low-cost, micro-spectrometers in the VIS-NIR and SWIR spectral ranges (price reduction: factor 10, production volume increase: factor 100).	2025	9
"Intelligent spectrometry" with embedded data analysis for rapid alert.	2030	9
Low-cost, micro spectral-imaging in the VIS-NIR and SWIR spectral ranges (price reduction: factor 100, high-volume production: > Mio units/years).	2030	9

Challenges and Route

Miniaturization and affordability of the measurements.

Some optical spectrometers are versatile and compact, but better mobility and robustness, and further miniaturization will allow more applications in the field. The effects of miniaturization are threefold. Firstly, small spectrometers enable local measurements in confined environments and these can be configured as an array of sensors in a network. Secondly, small spectrometers are portable and can therefore be used on the spot anywhere where needed. Finally, small devices open the door for drastic cost reductions and volume production. These three effects reinforce and will create new volume applications and markets.

Need to measure in real-time and in-line.

Industry is changing from off-line quality measurements towards real-time measurements at the production line. Tissue and waste materials are by nature heterogeneous and cannot be fully differentiated with (multi-spectral) imaging techniques. Most current spectrometry methods are performed through off-line measurements, requiring sample preparation and analysis in a lab environment. These methods are time-consuming, expensive and require users skilled in analytical spectrometry to perform the analysis. Therefore companies are looking for compact and robust spectral sensors and efficient data collection methods.

4 Health

The missions in the KIA "Gezondheid en Zorg" are:

- Mission I - Leefstijl en leefomgeving
- Mission II - Zorg in de leefomgeving
- Mission III - Mensen met chronische ziekten
- Mission IV – Dementie

For the Chemical Sensing and Enabling Technologies section of the Topsector Chemistry, many of the contributions are generic and do not apply to one mission only. There is quite some overlap from the technology side. Therefore, where applicable, the missions for which proposed activities are valid will be mentioned on the spot.

Quality of life (QoL) refers to the general well-being of individuals and societies. Important aims are to keep people healthy as long as possible, and to enable people in need of care to live a high-quality life in their own environment. Personalized (nano)technologies play an important role in achieving these aims, by monitoring personal biochemical health status and by enabling targeted and personalized drugs and food.
This chapter discusses the required innovations in chemical nanotechnology and devices in order to:

- Diagnose, monitor and stratify people; e.g. by measuring samples, such as liquid biopsies from people, or by measuring directly on people, e.g. on the skin or via a catheter (***Missions I, II, III, IV***).
- Treat patients; e.g. by drug delivery, regenerative engineering, neurostimulation (***Missions II, III, IV***).
- Increase efficiency in drug development and nutrition development; e.g. reduce/replace/refine use of animal models (3R), faster into human; human disease and organ models on a chip ("Organ on Chip") (***Missions II, III***).
- Synthesize and characterize novel "biological" drugs and specialty nutrition; as sole active ingredients and/or novel targeted or sustained release formulations (***Missions II, III***).

Technological innovations are needed (***Missions I, II, III, IV***) in the fields of:

- Novel materials & devices; e.g. for biochemical sensing technologies (in-vitro, in-vivo, minimally invasive), micro/nano-technological synthesis devices and for miniaturized Point-of-Care devices, in which assay complexity is solved by the device rather than a bulky instrument. This latter aspect requires precise control over surface properties allowing accurate flow and timing control.
- Novel fabrication & inspection technologies; e.g. for the development of functional materials, coatings and devices, with control on the nanometer length-scale
- Novel tools and methodologies for R&D, (i) to characterize complex molecular systems and interactions, novel drug and food delivery systems and biofunctional surfaces and interfaces; (ii) to model and understand the body response to compounds, materials and devices, e.g. by realizing Organs on Chip
- Novel methodologies to upscale microfluidic devices for production of medication and food ingredients, e.g. emulsions for targeted delivery purposes.

Cases

Bio-active sensing and actuation devices

Task

In the coming 10 years groundbreaking developments are expected to occur at the interface where nano-micro devices and complex molecular systems interact with biological systems. This will lead to highly sophisticated devices that are able to function with and within live biological systems. Novel bio-sensory and bio-actuation functionalities are expected, resulting from developments in bionanotechnology, biophysics, supramolecular chemistry, nanophotonic sensors, and regenerative medicine. Potential embodiments include smart patches, smart fibers, smart probes, smart catheters, smart implants, etc. The most advanced systems will combine and integrate molecular-based sensing and actuation principles of physical and (bio)chemical nature. Examples are: real-time sensing on the body or in the body; accurate drug administration using real-time data as an input; neuronal stimulation based on objective signals from the body and/or the environment; point of care diagnostics and monitoring (e.g. in Personalized/Precision Medicine); critical care monitoring; etc.

Example of a small sensor that continuously monitors the biochemical status of a person

A rapidly developing field in healthcare is the field of immunology, with new treatments and diagnostics being introduced based on the immune system. Presently, the inflammation status of patients is monitored by recording symptoms such as fever and blood pressure, and by measuring inflammatory markers using laboratory-based tools. However, the symptoms are not specific enough and laboratory-based testing procedures are slow, with data becoming available only after a day, which is unsuited for monitoring the markers of rapid inflammatory response. The present-day procedures are inappropriate for patients who can rapidly develop life-threatening conditions, such as cytokine release syndrome, a condition that occurs in patients with Covid-19 and patients receiving immunotherapies. Another important application is to measure and regulate drug levels, e.g. in case of antimicrobial therapies, for more effective life-saving treatments and lower risks to cause antimicrobial resistance. Also, devices for immunomonitoring would allow patients to be released from the hospital earlier, e.g. after having received an immunocompromising or a surgical treatment. Thus there is a clear and urgent demand for sensing tools to continuously monitor the condition of patients.

Goal	Year	TRL
Biomarkers (proteins, drugs) are measured in the laboratory	2020	9
Biomarkers are measured near the patient (POCT = point of care testing, individual samples are taken and measured)	2025	6
Biomarkers are measured continuously, samples are automatically taken via a medical device, e.g. via a catheter (continuous monitoring)	2030	6
Biosensors are worn on or in the patient (wearable, insidable)	2040	6

Challenges and Route

To accomplish this task collaboration of experts in the fields of device technology and chemical biology can be valuable. Device technology deals with the realization of novel device functionalities and related miniaturization and integration; partners can for example be found within the Top Sector HTSM, more specifically the roadmaps Nanotechnology, Photonics (linked to PhotonDelta, a national initiative financially supported by the (local) government with a European ambition - https://www.photondelta.eu/) and Advanced Instrumentation. In the field of chemical biology, chemical approaches are developed for biological systems. In The Netherlands we have excellent chemical biology groups (see e.g. Zwaartekracht Functional Molecular Systems www.fmsresearch.nl, and the NL Research School of Chemical Biology www.nrscb.nl). Furthermore, the Netherlands Institute of Regenerative Medicine (www.nirmresearch.nl) studies how human cells and tissue interact with materials and devices, and methodologies developed to understand such processes on different time- and length scales. Research collaborations of these different parties would be a great opportunity to focus on the interface between biochemical/biophysical devices and biological systems, which would also be of interest to large companies and SMEs operating in the field of materials, biotechnologies or medical technologies.

Scientifically, technologies could be developed to sense and control living systems in-situ and in real time. For example, small biochemical sensors integrated into medical devices and disposables, which are in contact with the human body and continuously monitor the biochemical status of patients. Materials and devices for drug delivery and for bio-mimetic stimulation. Systems for comprehensive biochemical profiling. Systems for closed-loop monitoring and treatment. In industry, novel products for biochemical patient (therapy) monitoring, drug delivery, neuro-stimulation and critical care monitoring could be developed. This can improve the added value of medication, therapy effectiveness and compliance, which would reduce the overall healthcare costs through disease management and early detection of exacerbation. Enable novel care models based on patient monitoring and decentralization.

Society could profit from these innovations by the introduction of personalized medicine, the possibility of early diagnoses and self-monitoring and improved therapy adherence. This in combination with the reduction of side-effects of medicine could reduce result in more people growing old healthy.

Possible topics

Bio-interfaces, passive and active anti-fouling interfaces, biomimetic interfaces, biodegradable polymers and interfaces, degradation-resistant interfaces (e.g. for GI tract), interfaces and nanoparticles for release of bio-actives, interfaces for control of body reaction.

- Synthetic-biological concepts for sensing and actuation, bio-inspired devices, nanosensors.
- Minimally-invasive bio-functional healthcare devices.
- Novel scientific analysis tools, for studies with high spatial and temporal resolution (e.g. studies with single-molecule resolution) and for high-throughput screening studies (e.g. to screen novel materials with many degrees of freedom).
- Fabrication methods, on the one hand top-down (cf. device technology community), on the other hand bottom-up (cf. chemical biology community).
- Characterization of thermodynamics, kinetics, and transport processes in complex interaction systems.

- Analysis of samples of physiological origin, e.g. blood testing, skin sensing, mucosal fluid testing, interstitial-fluid testing, tear sensing.
- Integrated devices featuring combinations of bio-inspired techniques with other techniques, e.g. combining synthetic biological sensing with sample transport via capillary flow.
- Sampling devices; chemical & biochemical lab-on-chip technologies; increase information quality and quantity from small complex samples, such as liquid biopsies.

Human disease and organ model systems on a chip

Task

The development of novel pharmaceutical and nutritional compounds is complicated due to the inherent complexity of the human body and the variability between people. Furthermore, for ethical reasons the testing of new pharmaceutical compounds on animals and humans should be minimized as much as possible, while cosmetic compound testing on animals recently has been completely forbidden. This calls for the development of sub-cellular, multi-cellular and multi-organ human model systems on a chip. Such human model systems can support scientific research on how the human body works, and can help to improve and accelerate the testing and development of novel pharmaceutical and nutritional compounds. In the future, even personalized model systems may become available, e.g. built from induced pluripotent stem cells (iPS technology), which allow creating functional organs tissues on chip possessing the genetic (disease) profile of the patient and thus allow the realization of *precision* medicine.

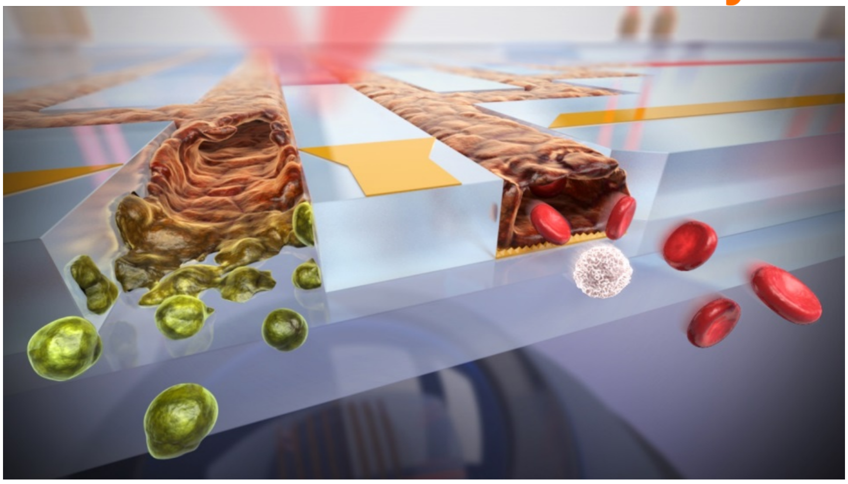
Goals

Goal	Year	TRL
Biomembrane / organelle / cell / multicellular system on chip	2025	7
Organ functionality on a chip / combination of organs / interacting organs mimic complex body function	2025	8
Transport processes in living systems, e.g. across membranes (artificial, biomimetic, biological), between cells, between cells and extracellular matrix, between cells and solid surfaces	2030	7
Minimal-system studies, i.e. what minimal system is needed to achieve a desired multi-cellular functionality	2030	7

Challenges and Route

The Netherlands has a leading position in Europe and plays an important role in the development of Organ-on-Chip technology and the applications of healthcare professionals (e.g. medical doctors, pharmacists). Chemical chip technologies (e.g. surface modification, biomembrane on chip technology, sensing on chip) and cell biological technologies will play an imminent role, while many technology solutions can be derived from earlier lab-on-chip developments. Novel methodologies and tools should be developed, for example, to understand how compounds interact with membranes, cells, and organs. A variety of tools should be developed ranging from high-throughput screening compatible methodologies for research to application dedicated equipment for personalized therapies.
The topic would partly fit within the Topsector LSH and HTSM, and Agrofood fields. Furthermore, the topic links to the MinacNed association, for micro/nanotech organizations (with a dedicated microfluidics/lab-on-a-chip cluster) as well as HollandBio for med/biotech organizations, including many drug development SMEs. The topic is the focus of the virtual hDMT (human Disease Model Technology) institute (www.hdmt.technology), which has been founded in 2015 and in which a crossover between device engineers, biologists, pharmaceutical and medical scientists, and nutritionists has been established.

Scientifically, multicellular human disease models and high-throughput organ-on-a-chip models should be developed. Interactions between organs and drug functionalities could be explored. Economically, the costs and time-to-market of novel drugs is currently very high and should be decreased drastically. Using precision medicine the effectiveness of patient treatment could be improved. Society will benefit from these innovations as personalized medicine will be available, side effects from drugs will partly be prevented and the need animal testing will be reduced. (***Missions I, II, III, IV***).


Artist's impression of microengineered iPSC-derived blood vessel structure with integrated microelectrodes for studying drug transport across endothelial blood vessel wall.

Microfluidic devices for synthesis of medicine

Task

Chemical and biochemical research increasingly exploit the use of fluidic microdevices for the synthesis of new compounds and for tailoring formulations to maximize the effectivity of the compounds. Microtechnologies and microfluidics allow for the synthesis of small amounts of high-value specialty products and allow controlled structure formation. Such technologies will enable the seamless upscaling from research to production ('scalable flow chemistry'), which will be very helpful for the emerging paradigm of Precision Medicine and for innovations in nutrition. Application examples are miniaturized (multiphase) flow systems for enzymatic cascade reactions, and the development of encapsulates for targeted compound delivery with sustained activity ('formulation'). This approach is valid for medication as well as for other sectors such as food, personal care, etc.

Goals

Goal	Year	TRL
Synthesis and formulation of pharmaceutical drugs, small molecules and biopharmaceuticals (active pharmaceutical ingredients, APIs), and food.	2025	9
Specifically encapsulate components on chip, encapsulation of food ingredients	2025	9
High-throughput screening of functionality of components used in formulation in combination with the active compounds	2025	9
Development of production technologies for nanotech-based targeted drugs and formulations	2025	9
Surface modification, multiscale modelling and rational design of formulations, interfacial design, functional nanoparticles, nanosomes, microdroplet chemistry	2025	9
Lab-on-a-chip/microfluidics based flow chemistry systems including (integrated) analysis/monitoring and process control	2025	9

Challenges and Route

The development of microfluidic synthesis and formulation devices requires a crossover between partners in micro/nanotechnology, chemical and biochemical synthesis, and biomedical sciences, with a key role for innovative high-tech SMEs. In the Netherlands many micro/nano and biotech SMEs have emerged, backed by world-renowned research groups at universities/institutes. The topic also relates to the Future Medicine Initiative (formerly Chemistry for Future Medicine) and the Netherlands Center for Multiscale Catalytic Energy Conversion (cf. Zwaartekracht MCEC). Furthermore, the topic links to the MinacNed association, for micro/nanotech organizations (with a dedicated microfluidics/lab-on-a-chip cluster) as well as HollandBio for med/biotech organizations, including many drug development SMEs.

Scientifically, microfluidic technologies for the synthesis of new active pharmaceutical ingredients (e.g. biologics by cascade reactions) and new formulation concepts (e.g. encapsulates) should be developed. To achieve custom-made nano-medicines an integrated and flexible production of formulated drugs must be pursued. Industry benefits from innovations to improve the added value of medication and food and a reduction of the time-to-market for drugs. Personalized medicine and the possibility of targeted drug delivery will have a large impact on the overall health and disease treatment of society.

5 Industrial Safety and Process Development

CSET-relevant key technologies (Table 1) such as advanced analytics and sensoring, data science, and modelling will play a crucial role in developing new processes and improving the monitoring and control in the (petro)chemical, agro/food, and pharmaceutical industries. Applications of improved and extended sensing in the processing industries will benefit the design of new processes (e.g. by improving chemical understanding) and the efficiency and sustainability of processes at plant-scale, but also their safety aspects.
To implement "Factory of the Future" and "Industry 4.0" concepts in practice, developments in key CSET technologies are therefore needed and proposed in this roadmap. Case studies describing the role of such technologies for industrial safety and process design are described below.

Cases

Industrial safety
Task
Industrial manufacturing operations must be organized, managed and executed in such a way that employees and assets are protected by minimizing hazards, risks, and accidents. Whereas employee behavior, company culture, and HSE regulations are major drivers for a safe industrial environment, there are technological opportunities and challenges related to CSET that will contribute to the enhanced safety of both the occupational and process/production aspects of future manufacturing. The term "Safety by Design" is at present an integral part of the European "Joint Technology Initiative" SPIRE, recognizing the importance to consider safety as an integral part of industrial design. To this end, chemical sensors and advanced enabling technologies with high specificity and sensitivity must be developed for fixed deployment both in and around a production process as well as for flexible use by operators in a plant environment.

Goals

Goal	Year	TRL
Wearable, portable, or fixed sensors for continuous air monitoring of specific chemicals of concern in a production environment, including ATEX (Atmosphere Explosible in French) zones.	2030	8
Standoff portable sensors for rapid identification of leaked chemicals (e.g. liquids, solids) in a plant or in the environment.	2030	7
Drone-based miniaturized sensors for environmental surveillance of chemicals, e.g. in case of inadvertent release or leakage.	2030	7
Handheld rapid identity testing of raw materials to prevent chemical misoperations.	2030	7
In-/on-line process analytical technology that completely avoids manual sampling from a process pipeline or reactor.	2040	7
In-/on-line sensing techniques, including soft sensors, that provide early warning signals for potentially hazardous process deviations or upsets.	2040	7

Challenges and Route
The main challenges related to sensing for industrial safety are *i)* the development of new and/or improved sensing mechanisms for chemically specific detection and *ii)* turning such sensing mechanisms into low-cost, rapid, robust, small and sensitive physical sensors. This will require tight collaboration between research groups and instrument developers and vendors (e.g. high-tech SME or larger vendors). A particular additional challenge is the development of sensors that work robustly in chemically demanding (e.g. corrosive) environments.
With the growing importance of artificial intelligence (AI)-based process control mechanisms also comes an increased reliance on data quality, which means that sensors and their data must be(come) highly reliable and robust.

Industrial process development

Task

Processing industries such as (petro)chemical, agro/food, and pharmaceutical are under continuous pressure to maintain or increase their competitiveness in terms of economic efficiency, sustainability, flexibility, and safety. To address this challenge, it will be crucial to rapidly and effectively design and scale up new and improved processes (Factory of the Future). In turn, this will fuel the need for a more fundamental understanding of raw material characteristics (which, increasingly, are complex bio-based materials), (bio)chemical pathways and their corresponding thermodynamics. Flow chemistry will have important added value in this regard by its ability to translate processes at nano- or micro-scale to those at e.g. pilot plant scale.

Goals

Goal	Year	TRL
Novel multi-model analytical technologies with ultimate chemical, spatial, and temporal resolution. For example, availability of miniaturized in-/on-line detection technologies for *in situ* measurement of reactants, intermediates, and products and catalyst behavior at different time and length scales.	2030	5
Availability of innovative micro-flow reactor technologies for gas-, liquid- and solid-phase chemistries. Advances in molecular modelling (incl. density-functional theory (DFT)), process modelling and chemometrics (incl. soft sensors) for improved chemical process understanding and control.	2030	7
Implementation of the "Factory of the Future" on the basis of flow chemistry in a variety of chemical production processes.	2040	6

Challenges and Route

Key in achieving the vision for the "Factory of the Future" using flow chemistry are smart analytical (nano)technologies which can create a more detailed understanding of chemical pathways and which are anticipated to be also applicable for larger scale flow chemistry. In general, the availability of in-/on-line analytical technologies will enable the characterization of chemical reactions and their catalysts at the spot, without time delay and without sampling demand or any other interference to the spot of information. Such developments in Process Analytical Technology (PAT) will become key enablers for realizing smart process control systems as envisioned by the Industry 4.0 platform. PAT sensors can be integrated into bigger modern process control systems such as Evonik's EcoTrainer, which is a standardized process control platform for use not only in pilot and production, but also for the very first chemical laboratory measurements. Thus, the sensors and derived new process control concepts can lead to a unification of the formerly different and separate stages and thereby lead to massive shortening of process development time. This is to go hand in hand with bringing in advanced molecular modelling (including density-functional theory (DFT)) and process modelling approaches (*in silico* experimentation) for improving our understanding of chemical processes and the way that such processes can be controlled. Also the increased interest in gas- and solid-phase flow chemistry is of importance and opens a new window in micro-reactor engineering, process modelling, phase separation (down-stream processing) technologies, and dedicated analytical technologies.

Apart from the search and implementation of new complex chemical processes, the increasing expectations from customers on "product quality" and the need for ultimate "reliability" of the complete production processes are regarded as decisive challenges. As an example, manufacturing of polymer-based biomaterials and chemically modified bio pharmaceuticals will face ever-increasing quality demands from regulatory bodies, also putting great emphasis on process reliability (PAT initiatives).