VLAG External Peer Review 2015 -2020

Summary

Word of introduction / summary by scientific director Prof. Dr Karin Schroën

In the year 2020, VLAG Graduate School reached the milestone of having 500 PhD candidates registered at the same time. The number of PhD candidates has been rising steadily in the last five years (see section 2.2.I and Appendix 5), and that also implies that the 'services' that VLAG provides are more important than ever. From the early days of VLAG some 27 years ago, one of the targets has been to provide high quality postgraduate courses for PhD candidates, and when looking back it is clear that both the quantity and quality of the courses has been steadily on the rise (see section 2.2.II), and also made to comply with current challenges that PhD candidates face. Besides scientific content driven courses, more and more skills driven courses have been offered by VLAG in collaboration with the five other graduate schools at Wageningen University. We feel that this is important to prepare our PhD candidates for their life-after-the-PhD, and thus co-develop professionals that are impactful within their profession and society as a whole.

Our PhD community is very diverse and international (see section 2.2.I). The PhD candidates are highly productive, and they contribute greatly to the scientific output created by the VLAG community. In general, our PhD candidates deliver PhD theses that contain at least four scientific papers that are either published, submitted, or available as thesis chapters. Topics they work on are very diverse ranging from fundamental research to highly applied work (e.g. in close collaboration with the Wageningen Research Institutes) within a very wide range of science fields (see VLAG Research Themes in Appendix 1). Our researchers are successful in acquiring funding from diverse and prestigious national and international funds (see respective self-assessment documents in Part B). This enables our alumni to contribute to all aspects needed to advance science, and bring these findings toward society as a whole, including industry.

Furthermore, our PhD candidates contribute greatly to teaching undergraduate students, both in assisting during laboratory and/or exercise sessions, and as co-supervisors of BSc and MSc thesis students (see section 2.2.III). In doing so, they experience the whole breadth of scientific work. It is good to mention that PhD candidate to research staff ratio within VLAG is rather high, and the requirements that tenure track system puts on our staff may also influence wellbeing of our PhD candidates, and thus is a constant point of attention. It is good to realise that this 'total package' is very demanding and needs constant monitoring. To achieve this VLAG has made an additional effort by hiring a PhD advisor in January 2021.

Although many things are going well, and we are proud of the level at which our PhD candidates graduate, we also feel that there is still room for improvement. This is also put forward in the WGS Vision on the Wageningen University PhD Programme (see Preamble III). We feel that in communication still steps can be made, be it communication between supervisor and PhD candidates, within the VLAG community as a whole, and also beyond. In general, PhD candidates are rather goal oriented, as are their supervisors, and this may take away from scientific development for which curiosity driven incentives are essential. Within VLAG we have taken this to heart and have put a number of innovations forward. To facilitate scientific discussions/communication, and inspire junior scientists, various initiatives were improved or introduced recently, such as: 1. Review procedure for PhD research proposals has become a constructive learning experience, 2. Live on-line expert lectures have brought VLAG community together in spite of COVID measures, 3. VLAG Open Round has built new bridges without burden of intricate selection procedures, 4. Renewed VLAG Fellowship programme will help opening many new doors, 5. VLAG Graduate Programme inspires young talents to seek their own ways in science, etc.

Over the years, VLAG has steadily developed from a more service-oriented organization that took good care of supplying PhD candidates with postgraduate courses of high scientific quality and courses that allow PhD candidates to develop general professional skills, to an organization that takes care of the well-being of PhD candidates from many different angles. Currently this is more and more geared toward empowering PhD candidates to take the lead and providing the setting for them to discover the kind of scientist they want to become. We make it our priority to keep VLAG and its 'services' up to par, in sync with current scientific climate, and in line with the ever-increasing demands that are put upon scientists. We will thus keep developing and anticipating on requirements to be met and remain successful in the research fields that we operate in, and sometimes even a little bit beyond, since that is what is required more and more from a scientist who wants to contribute to a sustainable healthy world. Quite a number of these developments take place within the realm of Wageningen Graduate Schools, which allows us to closely work together with the other five graduate schools to co-develop new initiatives, and strengthen our collaboration that serves as a sound foundation for support to our community.

VLAG Research Theme 1:
Chemistry for Life Sciences and Biobased Economy

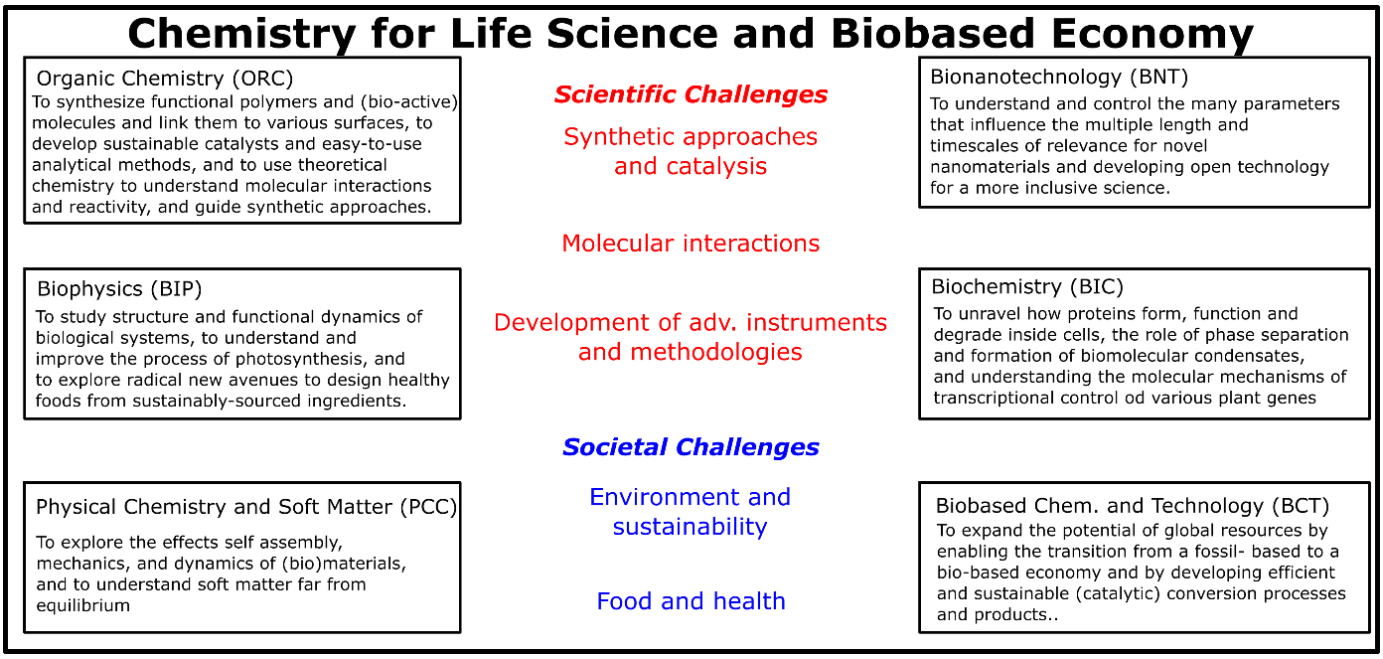


Figure 1 Chair groups member of our theme and a brief descirption of their scientific and societal topical areas

Case 1: Strengthening Chemistry & Physics

In 2019 WUR was granted a proposal within the Sectorplan framework to strengthen the beta-sciences at Wageningen University, enabling the opportunity to hire 9.0 FTE of scientific staff as a Tenure-Tracker, of which 8.0 FTE in our Research Theme within Chemistry, Physics and at the interfaces of these disciplines. The Chemistry focal points are 'Bio-active Surfaces' and 'Smart Polymers', while 'Biophysical Imaging & Spectroscopy' and 'Complex Soft Matter' are the focal points of Physics. The table below summarizes the topics that are part of this Sectorplan-related investment, which aims to link existing expertise and infrastructure with what our cluster considers core scientific areas in the next few decades.

Chemistry	Chemistry ⇔ Physics	Physics
Surface-bound Analytical Chemistry (ORC & PCC)	Soft Matter out of Equilibrium (PCC)	Physics of Photosynthesis (BIP)
Synthetic Biointerfaces (ORC)	Nano Magnetic Resonance (BNT)	Microstructure and dynamics in complex soft matter systems*
Green Chemical Synthesis (BCT)	Theoretical Surface Chemistry (ORC & BCT)	Computationally Designed Soft Matter (PCC)

*Part of Research Theme Food Science & Technology

Case 2: Open Science databases foster collaboration

Open Science is a matter of importance to our theme. We have developed open science on several fronts: PCC and ORC co-developed data management protocols that include descriptions and information ranging from labeling methods all the way to where and how data can be published online, and how they can be safely shared. As Open Science and related FAIR principles are an active area of development, all chair groups of our theme have always been represented at meetings where the Wageningen Data Science Competence Center (WDCC) discussed Open Science with stakeholders. This has led to concrete involvement of WDCC in the writing of for example the data management plan of the PCC-led ITN "CALIPER" and support from WDCC in getting PCC data published on Dryad. We are currently exploring options to start using YODA for certain research projects, which was introduced to us via WDCC.

We actively include data management considerations in our teaching. For example, the PCC course Advanced Soft Matter has lab journal management as a concrete learning goal. We teach our students data management standards that have emerged at other Dutch research institutes such as AMOLF.

Finally, we share our successful data management practices with others. For example, the SURF ResearchDrive facility, which greatly facilitates sharing of research data at reasonable costs, is now being adopted by other WUR groups as well.

Case 3: Exposure of PhD candidates to international developments in Chemistry

In 2017, our theme started a new initiative called the Wageningen University & Research Chemical Sciences (WUR-CS) colloquium series, which brings together chemistry groups of WUR with the specific aim of attracting world-class speakers to Wageningen to give seminars. We identified that our PhD candidates should have additional exposure to international developments in Chemistry. While PhD candidates have opportunities to travel to conferences, by bringing seminars to them, we increase their contact and access to expert speakers. This enables PhD candidates to ask questions, to network toward possible postdoctoral appointments, and to gain insight into chemistry areas beyond their individual PhD project. We attracted outstanding (inter)national speakers to our campus, including Nobel prize winners. Speakers included Prof. Bert Weckhuysen, Prof. Fraser Stoddart, Prof. Pascal Jonkheijm and others. This WUR-CS effort is still in development which has been affected by the pandemic.

Summary Research Theme 1

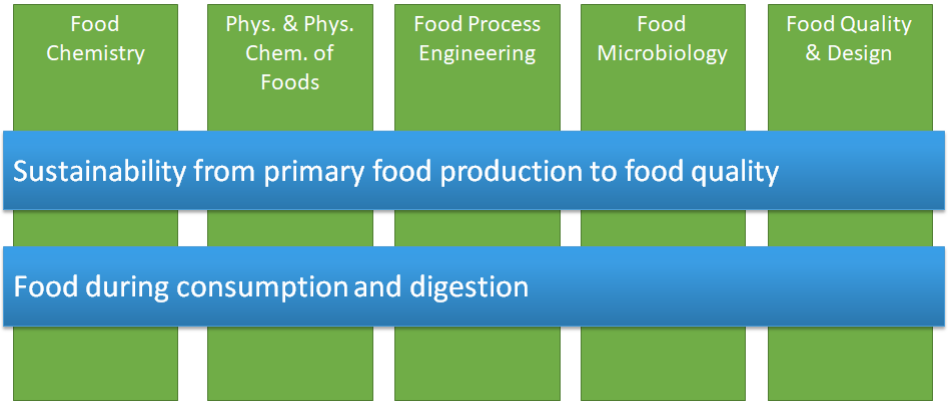
The theme "Chemistry for Life Science and Biobased Economy", comprising the chair groups of Biochemistry, Biophysics, Bionanotechnology, Bio-based Chemistry and Technology, Organic Chemistry, and Physical Chemistry and Soft Matter, focuses on understanding and improving the quality of life through addressing fundamental and applicable questions related to the chemistry of (bio)(macro)molecules. This mission is achieved through research along three lines: (1) synthetic approaches and catalysis of sustainable building blocks and greener synthetic and catalytic processes; (2) molecular Interactions and mechanisms that lead to self-assembly interactions of (bio)molecules on different length and time scales; (3) development of advanced instruments and methodologies from open technologies to cutting-edge instruments to study molecules and molecular interactions.

Our fundamental and applicable studies are at multilevel scales, from nanometres to centimetres, and range from natural products, such as proteins, to artificial materials such as nanoparticles. Progress in our molecularly oriented research depends strongly on the development and application of advanced instrumentation and methodologies, where the chair groups of our theme are at the forefront. Over the past 6 years, our theme has grown significantly in new research directions through existing and recently appointed 14 staff members, and via the expansion and upgrade of our experimental facilities for spectroscopy and microimaging, *i.e.* the Wageningen MicroSpectroscopy Research Facility and MAGNEFY. Our fundamental research addresses questions regarding, among others, synthetic approaches, and catalysis for bioeconomy, molecular interactions including hierarchical complex formation and nanomaterials, the biological roles of protein phase separation, non-equilibrium soft matter, involvement of specific proteins in prokaryotic immunity and deep phenotyping of plants, and the development of advanced instruments and methodologies. Our applicable research includes, for example, the study of novel natural and synthetic (nano)materials and the shifting from a fossil fuel-based economy. Within these areas, our theme has secured large amounts of funding from diverse sources at both the national and the European level. We have expanded existing laboratory facilities by new experimental equipment developed by both existing and new staff, with a strong focus on state-of-the-art technology and open science. Open Science is important to us. We not only published open access papers in high-quality scientific research journals like *Science, Nature (Chem., Comm., Mat.)*, *ACS Nano*, *Adv. Mater., Angew. Chem., J. Am. Chem. Soc.,* Proc. Natl. Acad. Sci., and *Phys. Rev. Lett.*, but also took extra steps to provide open databases, published open-source codes and full instructions on open repositories. We are also active in the development of open technologies, which are smaller in scale and cost less than, for example, our other expertise in NMR and microspectroscopy instruments. Additionally, in the last years WUR has become a partner of the 4TU. In this collaboration, our theme focuses on core topics such as AI, soft robotics, big data, and image analysis, which will expand opportunities for our research and consequent development of new teaching directions.

Our scientific research challenges are intrinsically linked to societal impact by asking key questions: how to improve sustainability and the environment, how to shift from a fossil fuel-based economy to a biobased one, how to produce synthetic materials more efficiently, how to improve the efficiency of nutrient and water management, how to improve health through food and (nano)medicine, how to improve sensors for health monitoring, and how to improve sustainable food production and reduce food waste. In these areas, our societal impact has been maximized, by collaborating with start-ups, SMEs and large companies to connect with real life applications; by being granted a total of 13 patents from 2015-2020; by organizing international conferences; and by educating 118 new PhDs and countless students to become well-educated, independent, professionals. We consider teaching as essential which is reflected in our consistent top ranking nationally over the last one and a half decades. We share multiple BSc and MSc courses in the WU curricula of molecular life sciences and biotechnology students. Our courses have become vastly more diverse and appealing to students reflected by the ever-increasing number of students that enrol in the WU curricula of molecular life sciences and biotechnology.

Our strategy for the coming period includes aiming for several targets. We will expand our research potential by establishing several fundamental research centers at WU, e.g., on the topics of photosynthesis and a micro- and nanolithography center. Additionally, while applied research is highly visible within WUR, we aim to increase the visibility of fundamental research, which is strong and exciting within our theme, through an increase in social media efforts. We will aid in our staff development by emphasizing a non-uniform profile of Tenure Trackers to highlight the diversity of our theme's talents. We will also continue the excellent quality of education within our theme, but to fully achieve this, high-end teaching facilities should be developed to release teaching overload from our own lab facilities. Within these outlined directions, we believe that our theme will continue to prosper.

VLAG Research Theme 2:
Food Science and Technology



Narrative 1: Mild processing routes applied to plant-based ingredients: a unit perspective
Mild processing typically results in ingredients that are compositionally more complex, containing for example proteins of different types, fibers, lipid droplets, and polyphenols. Functional synergies have been established in such complex mixtures already by Van der Goot et al. [2016].

> van der Goot, Atze Jan, Pascalle JM Pelgrom, Jacqueline AM Berghout, Marlies EJ Geerts, Lena Jankowiak, Nicolas A. Hardt, Jaap Keijer, Maarten AI Schutyser, Constantinos V. Nikiforidis, and Remko M. Boom. "Concepts for further sustainable production of foods." Journal of Food Engineering 168 (2016): 42-51.

As a unit we have built on this finding in various ways. For example, in the case of yellow pea, where albumins, which are often discarded in traditional extraction processes, are excellent foam stabilisers and can have a synergistic interaction with globulins to improve the stability of emulsions. The synergistic interaction was quantified in terms of differences in interfacial meso-structural and rheological properties. The significance of the meso-structure has been proven to exist for a range of differently sized moieties, ranging from proteins to polymers and nanoparticles, using a combination of advanced experimental techniques, simulation and analytical theory. This proof has resulted in an article jointly published by PIs from FPH, FPE, the Advanced Innovation Centre for Food and Nutrition in Beijing, and the Material and Polymer Physics department at ETH Zurich. The article shows how in-plane interactions induce the formation of heterogeneous interfacial meso-structures, which result in solid-like visco-elastic behaviour and dynamic heterogeneity, and identifies momentum transfer between bulk and interface as a dominant mode for surface stress relaxation, a mode which until now has mostly been ignored in experimental surface rheology. Such behaviour is crucial to understanding the stability of interfaces during processing and in a product. Thus, the findings enable to identify processing routes optimising specific multi-functionality using one ingredient base, and a better design of complex meso-structures and concomitant effects on macroscopic material properties.

> Leonard M. C. Sagis, Bingxue Liu, Yuan Li, Jeffrey Essers, Jack Yang, Ahmad Moghimikheirabadi, Emma Hinderink, Claire Berton-Carabin, Karin C.G.P.H. Schroen, "Dynamic heterogeneity in complex interfaces of soft interface dominated materials", www.nature.com/scientificreports/

Similarly, we identified synergies in three-dimensional gelation of complex mixtures, and understood according (micro-) phase behaviour in terms of the molecular interactions. In connection to this work, we mention the usefulness of microfluidic techniques for quickly screening foam and emulsion functionalities of complex mixtures and investigate timescales from microsecond to second. The work highlights one of our unique abilities to span a large range of time and length scales to provide mechanistic understanding of process-structure-function relationships for any type of ingredient. In the future the above insights on complex mixtures can be combined with insights obtained in parallel during this review period on survival strategies of food borne pathogens from molecular to ecological level, to reduce food risks in such more sustainable food production routes.

Similarly, for similar types of products a multi-scale approach has been applied starting from the chemical perspective, in unravelling the oxidation chemistry to fine-tune lipid oxidation pathways, which can destabilise emulsions and produce off-flavours. NMR spectroscopy has been implemented as an "early warning system" for lipid oxidation, which allows detection of lipid oxidation in days rather than weeks. High-end imaging approaches have facilitated detailed insights on the chemical / interfacial / transport interplay in food emulsions. By truly understanding the various phenomena underlying lipid oxidation, building of mechanistic models to predict oxidative stability will come within

reach, and eventually facilitate the formulation of sustainably produced plant-based foods with improved chemical shelf-life and taste.

Merkx, D.W.H., Delic, F., Wierenga, P.A., Hennebelle, M., and van Duynhoven J.P.M. (2019) 31P-NMR assessment of the phosvitin-iron complex in mayonnaise. Magnetic Resonance in Chemistry 57. 540-547.

An in-situ sustainable process for ingredient formation is fermentation, where the control of complex composition and functionalities of microbial communities forms the challenge. Hereto, strategies to engineer starter cultures with and without advanced genetic techniques have been developed, expanding routes to produce starter cultures based on existing industrial and artisanal dairy, pulses, and cereal and other plant-based fermentations found in the Western world, Asia and Africa and thus aiding in alternatives of sustainable production methodologies (see reference Moonga). Also, solid-state fermentation of mildly fractionated chickpea protein was used to deplete antinutritional oligosaccharides, enhancing nutritional value in a sustainable way, with high yield and also good technical functionalities (see reference Xing)

Moonga, H. B., S. E. Schoustra, J. van den Heuvel, A. R. Linnemann, M. D. Sainur Samad, J. Shindano and E. J. Smid. 2020. Composition and diversity of natural bacterial communities in mabisi, a traditionally fermented milk. Frontiers in Microbiology 8:1816.
Xing, Qinhui, Susanne Dekker, Konstantina Kyriakopoulou, Remko M. Boom, Eddy J. Smid, and Maarten AI Schutyser. "Enhanced nutritional value of chickpea protein concentrate by dry separation and solid state fermentation." *Innovative Food Science & Emerging Technologies* 59 (2020): 102269.

In addressing sustainability across larger parts along the food chain, a techno-managerial research approach was developed and connected to food quality parameters that are accessible to the other disciplines within the unit (following up on the group's initial educational development activities, thus exemplifying the education research nexus). This approach is now tailored towards emerging issues as fraud and authenticity and was also explored using for the first time in the food domain a system dynamics modelling approach. In addition, the food design strategies along the chain were applied to many cases in transition countries in Africa, South America and Asia, leading to the completion of more than 10 PhD theses.

A systems approach to dynamic performance assessment in new food product development Horvat A, Behdani B, Fogliano V, Luning P.A. (2019) Trends in Food Science and Technology 91. - p. 330 - 338.

Narrative 2: From food structure to perception and digestion: a unit perspective
We focus for our second research line on sensory perception, food intake regulation and food digestion, all in relation to food structure. Digestion and nutrients availability are influenced by structural characteristics of foods such as the network of cell walls in plant-based foods. Food structure provides signals for sensory perception and liking during food consumption. This information can be used to design foods that modulate oral processing behaviour and, by those means, regulate energy intake.

On consumption, we demonstrated that fast eaters do not compensate for their shorter eating duration by chewing more efficiently but are comfortable swallowing a less broken-down bolus than slow eaters. The differences in oral processing behaviour between fast and slow eaters lead to differences in bolus properties causing differences in dynamic texture perception. For the first time we have shown that inter-individual differences in dynamic texture perception can be explained by differences in eating behaviour. This shows how oral processing behaviour is important for sensory phenotyping of consumers. This work is the result of a collaboration between FQD, WFBR and the Division of Human Nutrition and Health. The respective paper has been cited 60 times (Scopus) and belongs to the top 10% of most cited papers in the field. Reversely, we also investigated how mechanical food properties determine oral processing behaviour (i.e. eating rate), for liquid, semi-solid and solid foods. Since eating rate is one of the key factors which determines food and energy intake, the publication demonstrates how manipulations of rheological and mechanical food properties can be used to potentially affect food and energy intake, even for foods that belong to the same product category (liquid, semi-liquid or solid). Based on the publication, guidelines have been formulated for food industry how food texture can be modified to regulate food intake. The publication is the result of a large collaboration between FQD, FPH, MCB (marketing and consumer behaviour), the Division of Human Nutrition and Health and AStar (Singapore). The paper belongs to the top 10% of most cited papers in the field. The findings on eating rate versus mechanical properties are relevant regarding the issue of consumption of so-called ultra-processed foods. This has

recently been associated with higher energy intake and higher prevalence of obesity. It has been suggested that the relationship between consumption of ultra-processed foods and obesity is confounded by eating and energy intake rate. We recently embarked on further studies to determine causal mechanisms how ultra-processed foods lead to higher energy intake and its association with obesity.

> Aguayo-Mendoza, M. G.; Ketel, E.; van der Linden, E.; Forde, C. G.; Piqueras-Fiszman, B.; Stieger, M. (2019) Oral processing behaviour of drinkable, spoonable and chewable foods is primarily determined by rheological and mechanical food properties. Food Quality and Preference 71: 87 - 95. https://doi.org/10.1016/j.foodqual.2018.06.006

Regarding in-vitro food digestion we have obtained a systematic understanding of the food micro-structural factors (affected by processing and/or type of ingredient) modulating digestion of macromolecules and micronutrients, the caloric intake from plant tissues, and the effect of processing on digestibility of plant matrix macromolecules. The explicit role of the plant-based matrix in digestion was captured for the first time in a mathematical mechanistic model for starch digestion from beans.

> A mechanistic model to study the effect of the cell wall on starch digestion in intact cotyledon cells Rovalino-Córdova, A. M., Aguirre Montesdeoca, V. & Capuano E. (2021) Carbohydrate Polymers 253, 117351

We have further expanded this work to understanding the role of the food matrix on availability of nutrients to the gut microbiota and, consequently, on the microbial community and its metabolism.

Similarly, the dynamics of the digestion of protein foods has been investigated using in vitro digestive methods, in which both the diffusive dynamics and the reaction rates of the acid and pepsin, were quantified. The protein gel density has a dramatic effect and does not just slow down the hydrolylsis, but also alters the type of enzyme kinetics, from a 'zipper' type to a 'one-by-one' mechanism. This work is now being quantified into a predictive, mechanistic model that combines the thermodynamics of the gel swelling and collapse, and the dynamics of diffusion and reaction kinetics, and extended towards in vivo measurements, using TD-NMR, in a collaboration with the WFBNR institute and the Human Nutrition division.

> Luo, Qi, Remko M. Boom, and Anja EM Janssen. "Digestion of protein and protein gels in simulated gastric environment." LWT-Food Science and Technology 63, no. 1 (2015): 161-168.

In considering the health impact of ingredients an important category are prebiotic oligosaccharides like human milk oligosaccharides (HMOs) and Galacto-oligosaccharides (GOS). GOS are for example used in infant formula to mimic the health effects of HMOs. GOS is a complex mixture of oligosaccharides and observed health effects are more and more shown to depend on the precise composition of the mixture. Thus, methodology to accurately analyse the composition of the mixture has become extremely important. By employing porous graphitic carbon (PGC) as the stationary phase in ultra-high-performance liquid chromatography-mass spectrometry (UHPLC-MS), we achieved identification of over 100 different GOS structures. Using NMR spectroscopy-validated structures of GOS trimers, MS fragmentation rules were determined which will further assist in rapid identification of individual GOS molecules. This novel method is crucial to understand e.g. the colonic fermentability and immune response of complex prebiotic mixtures like GOS since the response of any such mixture depends on the specific (isomeric) structure and concentration of the individual oligosaccharides present. Collaborating with e.g. WUR Human Nutrition, Microbiology, Host-Microbe Interactomics and UMCG, this technique provides to pinpoint the bioactivity of the entire mixture down to the molecular level of individual compounds. This research will be continued by a PhD student employing the recently installed high-end CYCLIC Ion Mobility Mass Spectrometer (first in Benelux) in oligosaccharide and glycan analysis.

> Logtenberg, M.J., Donners, K.M.H., Vink, J.C.M., van Leeuwen, S.S., de Waard, P., de Vos, P., and Schols, H.A. (2020) Touching the high complexity of prebiotic vivinal galacto-oligosaccharides using porous graphitic carbon ultra-high-performance liquid chromatography coupled to mass spectrometry. J. Agric. Food Chem. 68, 7800-7808.

Summary Research Theme 2

The Research Theme Food Science and Technology is addressed by the research unit that comprises the chair groups Food Chemistry (FCH), Physics and Physical Chemistry of Foods (FPH), Food Process Engineering (FPE), Food Microbiology (FHM), and Food Quality and Design (FQD). The research unit aims to be the world's leading unit of food science disciplines, by combining their joint expertise in all five disciplines with world class facilities into a centre that can work cross-disciplinarily to (i) create novel mechanistic understanding and invoke new principles to pro-actively facilitate our society and (ii) to tackle the challenges of turning the world's harvests into safe, healthy and enjoyable foods for our changing populations, for decades to come. Two major interconnected and multidisciplinary research lines exist. The first is *Sustainability from primary food production to food quality,* focussing on generating new mechanistic understanding and technologies that will allow to minimise food production-associated environmental impact and to reduce or reverse climate change, while at the same time ensuring sufficient food for a growing world population. The second main research line is *Food during consumption and digestion,* which, by integrating with the Human Nutrition and Health unit aims to quantitatively understand the sensory and digestion characteristics of foods, to maintain/improve the sensory performance of foods and of macro- and micronutrient bioavailability, and to adapt to the specific uses of consumers or groups of consumers. We have taken the scientific lead in forming consortia and strategically choose topics that jointly and congruently build our expertise. As an example of coherently building expertise together, we mention the major activities tailored around mild processing of plant-based materials into food products as studied on macroscopic, mesoscopic and molecular length scales, with a joint, unit spanning effort of 29 PhD candidates, making use of several funding routes (NWO, Top consortia for Knowledge and Innovation – TKI, several large, strategic consortia such as TIFN, ISPT and SFI). This and other unit-wide initiatives exemplify the unit's shift toward acting as one research unit, which makes that we are well positioned to continue to lead in the transition towards plant-based (protein) foods. We are investing strongly in our future strategy and have obtained significant funding in newly identified programs and in human resources (in part by means of government funded Sector plans of Physics and of Technology, and Van Rijn funding), making our scientific staff much better balanced in terms of age, thus better ensuring our long-term continuation.

Our unit has obtained an average Field Weighted Citation Impact of 1.42, i.e., clearly higher than the world average. It is quite stable during the evaluation period and the output quantity and quality of our unit is visible from the 1222 publications of which 15% belong to the top 10% most cited. About 50% of our work is in international collaboration, which illustrates the international character of the area and our reputation in the field.

We have generated 16 patent applications, and many contributions to professional/general-public books, a movie, articles for professional and popular science magazines, and advise to high-schools. We have been giving training-course lectures and workshops to specific local stakeholders in The Netherlands and abroad, and, explaining our science areas to primary school and high school students. We developed a MOOC on Food Safety, and placed knowledge clips on YouTube (some receiving more than 1000 views). We have been interviewed and consulted for magazines, newspapers, radio and television (in total roughly 230 times) on a variety of topics, among which the Italian science program "Superquark" on food intake and oral processing, national 8 o'clock news on meat analogues, food fermentation, and nutritional quality of Dutch traditional foods. We are consulted by ministries, and are member of governmental advisory boards and of research quality evaluation committees of international science departments.

Our future strategy encompasses 6 major future programs along three dimensions: scientific, socio-technological and advancement of enabling technologies. Within the Sustainability research line we will extend our understanding of the dynamics caused by the transition towards plant and other raw materials, throughout the total supply chain, which will include the complete use of the materials, but also interaction with consumers, and socio-economic networks (program 1). We will also extend our efforts into a program on mobility and growth of food-associated micro-organisms in food matrices, existing, or newly arising (program 2). Our shift to new raw materials, be they plant based or from novel sources, has great impact on both sustainability and the digestion and sensory experience, and thus fits in both research lines. Therefore, we will extend our efforts on "multi-scale understanding of novel plant-based food materials" to support the transition towards plant-based diets, fermented foods, enzyme-produced foods, dairy-plant hybrids and variability in sourcing materials (program 3). Related is the program on "novel food concepts based on new and synthetically produced sources", including fermentative production and synthetic cell production of new food ingredients or individually desired molecules, such as, for example, whey proteins from non-animal cells (program 4). Within

research line 2 we will continue and widen our efforts on the dynamic interplay between physiology, food structure properties and sensory perception (program 5), and digestion (program 6). The two research lines remain connected by means of the leading role of multi-scale dynamics.

Our current situation in terms of infrastructure, expertise, collaborative and creative culture has never been better, and we have good opportunities to continue investing in the cutting edge. The unit has great opportunities including nucleating gems of science to further build on its positioning and thus confidently looks forward to the future.

VLAG Research Theme 3:
Human Nutrition and Health

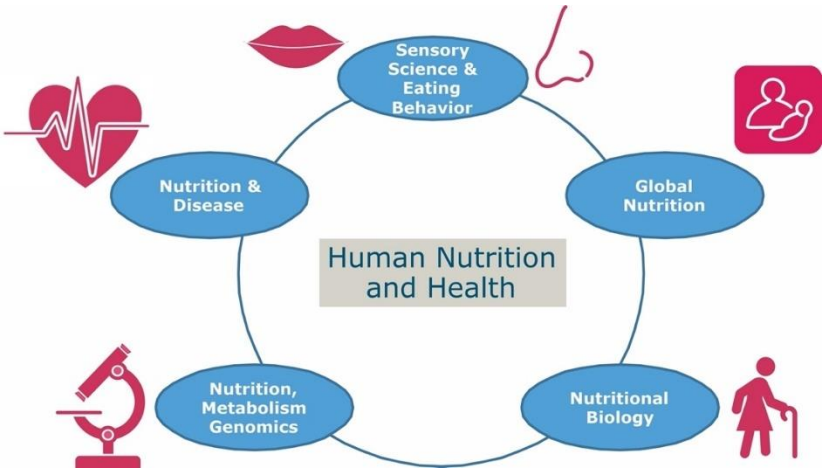


Figure 1 Chair group structure of the Division of Human Nutrition and Health

Several scientific and societal success stories are presented as narratives from each of the chair groups below, alongside a discussion on key publications supporting the narrative. Additionally, chair groups frequently work collaboratively on cross-cutting research projects, supporting the unit's intention to perform integrated, systems research covering multiple aspects of human nutrition. This is described in the 6th narrative on obesity.

Narrative 1: Understanding the role of lifestyle factors in disease risk populations

Key societal and scientific challenge: Cancer and cardio-metabolic disease are leading NCDs that are highly prevalent in the population at large, especially after the age of 50. As our population ages, our society will be increasingly confronted with the need for more effective prevention and rehabilitation from these diseases. A critical research question is: *to what extent do lifestyle factors, particularly diet and exercise, play a role in the recovery from cancer and cardio-metabolic disease?*

Research activities and scientific approach: HNH has been committed to studying the role of lifestyle factors in disease recurrence and mortality among large cohorts of patients previously diagnosed with colorectal cancer and myocardial infarction. The COLON study was a prospective cohort study of more than 2000 colorectal cancer patients with a follow-up after diagnosis of about 10 years. The Alpha-Omega Cohort study has followed ~4500 participants who previously experienced a myocardial infarction. Participants were assessed using an array of techniques in addition to baseline and follow-up disease outcomes.

Relevant scientific output: The COLON study found that healthier lifestyles and body composition were associated with a lower all-cause mortality, and occurrence of fatigue. Additional studies of the cohort showed that micronutrient status (magnesium, vitamin D, folate) is associated with complications of therapy, inflammation and mortality in colorectal cancer patients. The Alpha-Omega trial has made critical insights into the role of diet in the kidney function decline seen in many individuals following myocardial infarction. Specifically, higher protein intake and a higher body mass were associated with a more rapid decline in kidney function, demonstrating the need for targeted dietary and weight-loss interventions. More generally, most individuals in the cohorts did *not* change to a healthy lifestyle following diagnosis and/or recovery, highlighting the urgent need for more effective lifestyle interventions in these populations.

Societal relevance and outcomes: Knowledge gained from these survival cohorts is extensive, including increased knowledge surrounding recommendations for those with a chronic disease, and insights into the determinants of behavioural change in those with chronic conditions. Based on the results of these studies, lifestyle intervention studies among individuals at high risk of cardio-metabolic disease and individuals with previous colorectal cancer are currently starting. Together with clinicians, dieticians, physiotherapists and behavioural scientists, HNH is working towards the design and implementation of sustainable lifestyle interventions which will ultimately reduce disease risk, improve prognosis, and increase quality of life in these populations.

References: PMID: 33677488, 33067775, 33134831, 32190892, 30768201, 33744039.

Narrative 2: Protein and resistance exercising in the elderly

Key societal and scientific challenge: Almost every country in the world is experiencing an increase in the number and proportion of elderly people. Aging is associated with a decline in muscle mass and strength, which can lead to a condition called sarcopenia. Sarcopenia is believed to be the result of a reduced responsiveness of the skeletal muscles to major anabolic stimuli, including food intake and physical activity. The key research questions for this line of research were: *how does nutrition interact with physical activity to influence muscle mass and strength, and what nutrition strategies can combat sarcopenia?*

Research activities and scientific approach: Several sequential programs on diet and muscle mass and function in older adults were initiated within the Top Institute Food and Nutrition (TiFN), entitled 'Dietary strategies to augment muscle mass and function: clinical benefits of nutritional interventions in the elderly', 'Muscle mass preservation: evaluate the impact of dietary strategies during energy intake restriction', and 'Muscle health and function'. All programs were full collaborative efforts between HNH (Prof. Lisette de Groot) and the M3 Research Unit at Maastricht University (Prof. Luc van Loon). The programs were carried out with input from several industrial partners, including FrieslandCampina, DSM, and Danone, and encompassed several intervention studies in the elderly. So far, more than 50 collaborative papers have been published.

Relevant scientific output: A critical outcome of these studies was the demonstration that protein supplementation increases muscle mass gain during prolonged resistance-type exercise training in frail elderly people. Based on this major scientific achievement, a follow-up project called ProMuscle in Practice was started to set up and implement guidelines on combining resistance exercise training and increased protein intake, to promote strength and physical functioning. For this project, a clinical trial was adapted to real-life care and community settings in the Netherlands, showing most effectiveness and cost-effectiveness (see key publication references below). Based on these results, industry partners of the project are developing and marketing protein-rich products for older individuals.

Societal relevance and outcomes: The ProMuscle in Practice project has provided the basis for the broader implementation of the ProMuscle protocol/guidelines across the Netherlands, with the potential to achieve broad impact in the health of elderly Dutch individuals. Once the project reaches the full- blown implementation stage, the primary responsibility will move to health and care professionals, municipalities (WMO-driven), municipal health services (GGD) and other organizations.

References: PMID: 25717010, 31948853

Narrative 3: CGIAR-A4NH Flagships Research Programme Food Systems for Healthier Diets

Key societal and scientific challenge: Poor quality diets are the root cause of all forms of malnutrition. Food systems are rapidly changing in low- and middle-income countries but fail to deliver access to healthy, safe, and affordable foods for all. In addition, food systems contribute significantly to environmental degradation. Given these challenges, the Food Systems for Healthier Diets (FSHD) flagship research program was established as part of the CGIAR Research Program on Agriculture for Nutrition and Health's (A4NH) and started in 2017, coordinated by HNH. The broad research questions were: *what types of food systems transformations can be employed to improve diets and address the burden of malnutrition, while safeguarding planetary health and reducing poverty and inequality?*

Research activities and scientific approach: Research moves along a deliberate trajectory from diagnosis and foresight analysis of national and subnational drivers of food system transformation, to testing concrete innovations and interventions, to scaling up and anchoring successful actions in collaboration with country stakeholders in Ethiopia, Nigeria, Bangladesh and Vietnam. Research activities focus on thorough food system analysis including development of a comprehensive set of indicators to measure food systems and their development pathways. Food system innovations and interventions research is focused on providing evidence for catalysing demand for protective foods such as fruits and vegetables requiring understanding of consumers, food choices and food environment characteristics.

Relevant scientific output: A set of analytical food systems tools, indicators, and frameworks are now available through the Food System Resource Center and the Food System Idea Exchange. These include methods to assess the food environment in general and for adolescents, and a World Index for Sustainable and Healthy Diet. Collaboration with the Ethiopian Public Health Institute and the FAO resulted in the development of country-specific food-based dietary guidelines. New evidence is generated for a suite of consumer-oriented innovations for healthier diets, such as: improving availability, accessibility, and acceptability for fruits and vegetables in Nigeria and Vietnam.

Societal relevance and outcomes: The national food system analysis described above is explicitly in-line with the implementation of the Dutch Policy on Foreign Trade and Development Cooperation, via the Royal Netherlands Embassy in the four focus countries. Aided by this project, the Government of Ethiopia and the Ethiopian Public Health Institute adopted the development of food-based dietary guidelines as a "flagship programme", necessitating 3 monthly reporting to the Ethiopian Parliament. The programme engaged and built capacity among stakeholders at national level to act toward building food systems that support healthier diets. Capacity building via enrolling 15 PhD students and via engaging young researchers from local universities in food systems works has been advanced to help develop future leaders in all four countries.

References: PMID: 31315863, 33396659, 33283419

Narrative 4: Taste and texture in food oral processing and energy intake

Key societal and scientific challenge: Overnutrition is on the rise in every global region. Understanding what governs the excess caloric consumption that leads to weight gain is key to re-designing healthier foods and diets. Our energy intake starts at the mouth. Accordingly, the critical research question is: *what properties of foods determine how much, and how fast someone eats?* This has historically been difficult to study in a controlled fashion.

Research activities and scientific approach: In recent years, HNH has pioneered the measurement of food intake and eating behaviour using novel approaches and technologies. Studies have made use of foods engineered to control for taste, texture, or caloric properties, coupled with advanced sensors and imaging techniques to assess eating behaviour. This has involved clinical trials, observational studies, and longer-term questionnaire-driven assessments.

Relevant scientific output: In the project 'Satisfaction', critical insights were made into the determinants of satiation; for example, that longer duration of oro-sensory exposure shortens the time until satiation, as do foods with a stronger sweet or salty taste; and that texture of foods is a more important factor than taste in determining satiation rate and intake. Combining brain Magnetic Resonance Imaging and hormonal measurements in the blood stream has also led to insights into brain signalling mechanisms involved in taste and satiation. The NQPlus cohort study is now taking this a step further and has compiled a database with the most frequently consumer foods in the Netherlands according to taste intensity.

Societal relevance and outcomes: Understanding precisely how food properties relate to eating rate and satiation, for different individuals and in different settings, directly guides food reformulation. This information is already being used to guide the engineering of foods which have similar taste, texture, and palatability to commonly consumed foods, yet take longer to be eaten or reach satiety sooner – thereby impacting caloric intake and overweight and obesity. Further research will focus on the large variation between individuals in eating rate and behaviour and connecting short-term eating behaviour to longer term measurements of nutrient status and energy balance in clinical trials.

References: PMID: 32320002, 28174138.

Narrative 5: The impact of obesity on the immune system

Key societal and scientific challenge: Obesity is a burgeoning health problem across the world. Obesity is associated with chronic low-grade inflammation, which is believed to importantly contribute to the pathogenesis of obesity and may also increase the risk of infectious diseases. In line with this notion, individuals infected with COVID-19 who are obese and/or suffer from diabetes exhibit a more severe course of the disease than infected individuals who are metabolically healthy. The core research questions were: *how do disturbances in metabolism influence the innate immune system, and how does activation of innate immune cells influence cellular metabolism?*

Research activities and scientific approach: This line of research was funded by the Heart Foundation, the Diabetes Foundation, and the Netherlands Organisation for Scientific Research. Studies were conducted in monocytes isolated from human volunteers, in macrophages obtained from mice deficient in the HILPDA gene, and in the corresponding live mice. A variety of molecular tools were employed including flow cytometry, metabolomics, transcriptomics, confocal microscopy, and Förster resonance energy transfer-fluorescence lifetime imaging microscopy.

Relevant scientific output: We found that exposure of human monocytes to microbial components profoundly influences intracellular metabolism of lipids. In addition, we observed that microbial components such as lipopolysaccharide promote the storage of excess lipids in so called lipid droplets. Our work led to the identification of a

novel protein that is associated with lipid droplets called HILPDA. We found that HILPDA promotes the storage of lipid in macrophages by suppressing lipolysis via inhibition of the ATGL enzyme.

Societal relevance and outcomes: It is expected that this line of research will yield new fundamental mechanistic knowledge regarding the pathophysiology of obesity and type 2 diabetes, on a cellular level. This has the potential to deliver new therapeutic opportunities to combat the detrimental effects of obesity on human health, such as emerging immuno- and microbiome-based therapies.

References: PMID: 27991883, 32049012

Narrative 6: Diverse interventions for obesity prevention and treatment

Key societal and scientific challenge: Obesity is characterised as a 'wicked' health problem, in that its many causes are both incompletely identified, and intricately connected to other biological and societal issues ranging from epigenetics to socioeconomic inequality to disconnected food chain actors. Many researchers world-wide are concerned with generating a causal systems map for obesity, providing a more complete picture of the intertwined biological, social, psychological, and environmental factors which influence an individual's energy balance. Here, the broad research question is: *which combination(s) of dietary and public health interventions can lead to overweight and obesity prevention?*

Research activities and scientific approach: This line of research is exemplified by several collaborative and consortium projects, which span the Sensory Science and Eating Behaviour, Global Nutrition, and Nutrition, Metabolism and Genomics chair groups. From a dietary treatment standpoint, the GRaandioos study sought to investigate the effect of whole grain intake on weight management. The Bellyfat study took the approach of randomized control trials of dietary interventions to manage abdominal obesity, combined with extensive phenotyping to examine effects on metabolic health. Finally, from a population epidemiology approach, BigO used mobile appls and smart phones to collect big data on children's health status, food intake, physical activity and surrounding environments, with the aim of identifying new intervention strategies to prevent childhood overweight and obesity.

Relevant scientific output: The dietary intervention trials in adults demonstrated that whole-grain wheat, relative to refined wheat, resulted in an increased diversity of gut microbiota, and healthier levels of liver fat. We also found that a high nutrient quality 25% energy-restricted diet is more beneficial for cardiometabolic health and weight loss than a low nutrient quality 25% energy-restricted diet. How do we ensure these healthy dietary patterns are adopted by individuals? The BigO project has collected data from over 5000 children across four European countries, linking body mass to both food environment and physical activity. The final phase of the project will identify behavioural profiles and features of the built environment that predict higher body mass.

Societal relevance and outcomes: Gaining insights into the composition of diets that reduce overweight and obesity, and their molecular mechanisms, will lead to the design and promotion of ideal diets for treatment and prevention. For these diets to be maximally effective and adopted by as many individuals as possible, including groups that are either disadvantaged and/or highly resistant to behavioural change, these interventions must be coupled to public health policy approaches targeting the built environment and physical activity.

References: 30541093; 33019308; 28529330

Summary Research Theme 3

The VLAG theme Human Nutrition and Health (HNH) is concerned with the immense 21st century societal challenges related to food and health. It overlaps 100% with the Division of Human Nutrition and Health (HNH) and is composed of the five chair groups Sensory Science and Eating Behavior (SSEB), Nutrition and Disease (NAD), Nutritional Biology (NB), Global Nutrition (GNU), and Nutrition, Metabolism and Genomics (NMG). HNH employs about 35 academic staff members and functions as a single academic unit with a common research infrastructure and office space, common administrative and research support staff, common social events, and shared leadership. Being united under one umbrella allows the five chair groups to operate more efficiently, coherently, and effectively in a competitive global research environment, fostering an excellent environment for interdisciplinary research in nutrition.

The mission of HNH is "To improve global health and well-being through better nutrition". HNH aims to understand how diet impacts human health and disease, thereby providing a strong mechanistic basis for evidence-based and sustainable dietary guidelines and policy. HNH studies the impact of what we eat on the health of individuals, populations, and the planet. This encompasses a broad variety of research domains, ranging from infants and adolescents to the elderly, from the healthy to the chronically ill, and from low-income countries to high-income countries. One of the unique features of HNH is the ability to cover the full causal chain: from the determinants of food choice, dietary assessment, detailed quantification and characterization of health and disease, the underlying molecular mechanisms of the impact of food and nutrients on the body, to the impact of our diets on planetary systems and environmental sustainability.

Since its inception 50 years ago, HNH has become one of the largest and most prolific academic units in the world dedicated to the study of nutrition. The unit has made significant advances in the study of the role of nutrition in disease-risk populations and the elderly, and has contributed to important frameworks for food systems transformations in several low-and middle-income countries. Moreover, fundamental advances have been made concerning the determinants of obesity, its physiological and molecular mechanisms, and cross-cutting prevention and treatment strategies. This success is also illustrated by a growing output of high-quality publications across the wide spectrum of nutritional science. For example, in the period 2015-2020, HNH has published 50 papers in the American Journal of Clinical Nutrition, the leading journal in the field. Besides having considerable scientific impact, the work performed at HNH also carries significant societal relevance and impact. Examples of its societal accomplishments are the tremendous success of HNH-coordinated nutrition MOOCs, the inclusion of the SLIMMER lifestyle intervention program into basic health insurance, the launching of the website https://www.voedingenkankerinfo.nl/, and the appointment of Prof. Marianne Geleijnse as vice-chair of the Health Council of the Netherlands. Staff members of HNH also frequently appear in the media and regularly participate in societal discussions surrounding nutrition and health.

HNH forms the center of a huge critical mass in Wageningen concerned with food and nutrition, providing an unmatched breadth of research lines and methods. HNH hosts an outstanding and modern infrastructure for nutrition research, including the possibility for controlled dietary interventions and eating behaviour observation. The high societal relevance of its research, its extensive network, the expanding collaboration across WUR, and a supportive and open research environment provide a fertile ground for continued success in the nutritional sciences.

It is increasingly recognized that human nutrition and health are an integral part of environmental sustainability goals. In the future, the research efforts of HNH will be increasingly inspired by the need to balance ecological, human, and economic health and vitality. The research topics where HNH aspires to make a difference in the ensuing years vary from explaining the inter-individual differences in response to dietary interventions and using this information to predict the individual response to diet, to the use of novel technology to better assess dietary intake, determining the sensory and biological attributes that drive overconsumption of foods and calories, positively influencing disease outcome and management via optimized nutrition, and balancing human and environmental health in wealthy and economically challenged populations.

VLAG Research Theme 4:
Biological Systems & Interactions

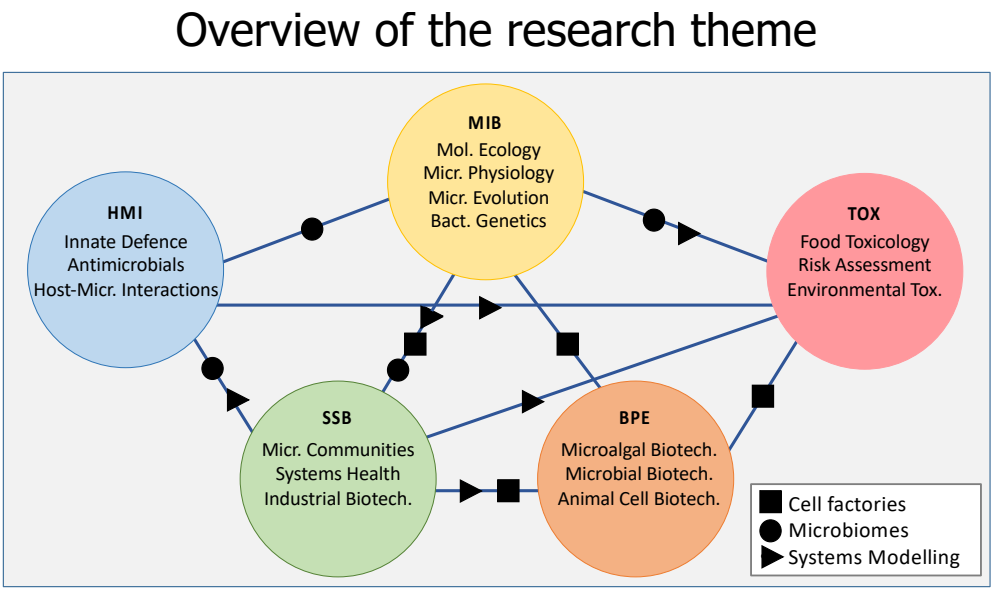


Figure 2 Overview of research theme, with their respective research lines, and the interactions between each chair. Note that "Mol" = Molecular, "Micr" = Microbial, "Bact" = Bacterial, "Tox" = Toxicology, "Biotech" = Biotechnology.

Case 1: CRISPR-nucleases - From bacterial defence systems to human gene therapy

After the breakthrough discoveries of the fundamental principles of bacterial adaptive immunity by CRISPR-Cas systems (multiple publications from MIB since 2008), and based on the demonstration of specific DNA targeting by bacterial Argonaute nucleases (Swarts et al. (2014) Nature), a revolutionary development has been encountered the last few years in which these fundamental insights have been used for the development of tools for dedicated genome editing. This has initially resulted in 3 patents (one on CRISPR/Cascade, and two on Argonaute), all of which have recently been transferred to Caribou, an SME in Berkeley (founded by Nobel prize winner Prof. Jennifer Doudna). In the past years, additional IP has been filed on a novel CRISPR nuclease (Cpf1/Cas12a; Zetsche et al. (2015) Cell, Zetsche et al. (2017) Nat Biotechnology), that has been merged with related patents of Prof. Feng Zhang at Broad Institute of MIT and Harvard, and has resulted in a joint licensing strategy (Editas Medicine). Later a series of patents has been filed on a thermophilic Cas9 (Mougiakos 2017 Nature Comms). The application of Cas9 nucleases and derivatives for various genome editing and regulation purposes is actively picked up by researchers throughout the theme. The discovery of thermophilic Cas9 opened up the possibilities for genome engineering in thermophilic host, such as Clostridia. The possibilities for genomic modifications of microalgae, which till recently were highly challenging, were improved by demonstrating genome-editing by the delivery of CRISPR-Cas riboprotein into the lipid-producing species *Nannochloropsis oceanica (*Naduthodi et al., 2019, Biotechnology for Biofuels), which was a collaboration between BPE and MIB. Within SSB a CRISPR interference tool based on a non-cleaving Cas9 (deadCas9) was developed to control the expression of multiple genes in the promising bacterial workhorse *P. putida (*Batianis et al., 2020, Microb. Biotech.). Further fundamental research into novel CRISPR-systems still reveals new insights and potential applications. Recently, a spin-off company of the theme (Scope Biosciences) started further developing CRISPR-based diagnostics based on a Type III CRISPR system to quickly (within ~30 minutes) detect DNA and RNA, for example SARS-CoV-2 RNA.

Apart from the impact in science, biotech and health the theme is active in societal outreach around this topic, including coverage in well-viewed talk shows on national TV (with Prof. John van der Oost as guest), and the set-up of educational programs at high schools, also supported from the Spinoza Award to Prof. John van der Oost.

Case 2: Understanding and exploitation of microbiomes – From gut to ocean

The advent of sequencing technologies in the last 15 years led to the improved capabilities of studying the microbial diversity in complex environments, such as human and animal gut, but also environmental locations such as marine environments and hot spring sediments. Studies of gut microbiomes have revealed groundbreaking insight on human and animal health. An example of that are studies on the gut bacterium *Akkermansia muciniphila*, which was isolated already more than 15 years ago within the theme and which through microbiome studies has been associated to healthy gut. Extensive studies of its genome, also at as a systems-level, including a proteomics study genome-scale metabolic model (Ottman et al., Applied and Environmental Microbiology, 2017) in a collaboration between SSB and MIB have revealed novel insights about the physiology of this organism. An important breakthrough with clinical relevance was the discovery of a specific protein of *Akkermansia muciniphila,* which can improve the metabolism of obese and diabetic mice (Plovier et al., 2017 Nature Medicine). This discovery led the foundation of the start-up A-Mansia in a collaboration with Universite de Louvain (Belgium), which focusses on understanding and commercializing this protein as a potential treatment for diabetes and obesity in humans (supported by several patent applications at MIB).

Studies on environmental microbiomes, such as marine microbiomes (led by Dr. Detmer Sipkema) revealed new insights on microorganisms that can potentially produce anti-cancer drugs, and marine microbiomes are also studied to improve sustainable aquaculture (further supported by a Marie Curie Training Network, EATFISH, 2020). The newly established group of Prof. Thijs Ettema studies environmental microbiomes, for example from deep sea sediments and hot springs, to increase fundamental understanding on the evolution, ecology and diversity of microbial life. The fundamental and applied studies in microbiome research require high-quality analysis of big (sequencing) datasets. Hence, MIB and SSB collaborated to further refine a publicly available pipeline for high-throughput sequence analysis NG-Tax 2.0 (Poncheewin et al, 2020 Frontiers in Genetics). Also, two data stewards were appointed by the theme to further support safe data storage and availability of data following FAIR principles.

TOX and MIB collaborate within the microbiome research to study the role of intestinal microbiota in degradation and detoxification of so-called advanced glycation end products (AGEs), considered to be involved in diseases associated with age, including neurodegenerative diseases.

In the past few years much of the microbiome research was funded by large grants, such as NWO-Gravitation (Soenghen Institute of Anaerobic Microbiology), ERC-Advanced Grants (Prof. Willem de Vos) and ERC-Consolidator (Prof. Thijs Ettema). The theme has focused on further consolidating this impactful umbrella of microbiome research in the coming years and expanding the collaborations and infrastructure toward this direction. Bridge funding (2018-2020) from NWO to establish a large-scale research facility for microbial communities was obtained in a collaboration of MIB, SSB and other partners outside the theme (including TU Delft). Recently, full funding was acquired for this large-scale infrastructure from NWO for the UNLOCK project (2020-2030). This structure will contribute to the plan of establishing a physical Wageningen Microbiome Centre by 2024, which will likely house several of the groups within the theme, as well as offer facilities to other scientists in the microbial community field.

Case 3: AlgeaPARC in action

After the first 5 years of operation (2010-2015), observations from pilot plant work and techno-economic models at AlgaePARC were used to develop focused research questions for the fundamental research program (Ruiz et al. 2016, Energy and Environmental Science). Examples of such projects are included in MIRACLES (metabolic pathway design and design of innovative reactors), a collaborative program with Unilever (mutation and selection), young scientist program Brazil (fluorescent assisted cell sorting), MAGNIFICENT (cell sorting and CRISPR-Cas in collaboration with Prof. John van der Oost MIB), NWO Building Blocks of Life (genetic modification and cell sorting in collaboration with Prof. Vitor Martins dos Santos, SSB). Increased genetic engineering possibilities lead efforts to test genetically modified microalgal strains in AlgaePARC for which permit have been obtained. The ambition is to have a shared strategy on microalgae biomass research in Wageningen University and Research and to bring research of the whole microalgal value chain together, from production to consumer. AlgaePARC has set WUR on the map for microalgal production and biorefinery and plays a central role in establishing this value chain, since it is at its start. It is now the moment to further extend the research to in depth characterization of microalgal biomass components (functionality and nutritional value), prototyping, sensory analysis but also to consumer and market studies, together with other science groups and chairs within WUR. In addition, a spin-off of AlgaePARC was established on Bonaire, in the Caribbean, to increase understanding and allow for comparison of cultivating microalgae in sunny regions with potential for higher productivities and the challenge related to lower photosynthetic efficiencies observed under high light intensities. Presently initiatives are taken to turn AlgaePARC Bonaire in a shared research facility Living Lab Bonaire. WUR initiated a Wageningen Biodiversity Initiative to work on nature inclusive solutions. Bonaire has a unique environment and biodiversity: it has the richest biodiversity in the Netherlands. WUR sees opportunities to build fundamental knowledge and expertise on nature inclusive solutions to create new business for nature inclusive solutions in Bonaire through research projects on agriculture, algae-aquaculture, food security and healthy diets, ecosystem performance and restoration, water quality, marine biodiversity research, ecological restoration, wildlife conservation and sustainable tourism (reef & fishery development).

Summary Research Theme 4

The overarching aim of the theme is to deepen our understanding of biological systems and their interactions, including their utilization to solve societal challenges. The theme consists of five VLAG-supported chair groups: Microbiology (MIB from hereon) Systems & Synthetic Biology (SSB), Bioprocess Engineering (BPE), and Toxicology (TOX). These five chairs host 29 full or associate professors, 10 senior staff members (including assistant professors in the tenure track system), and further 27 postdoctoral researchers and about ~150 PhD candidates.

Our research combines fundamental studies of biological systems with re-engineering and application in novel technologies. Throughout the theme, multiple scientific methods are combined to answer research challenges from single cell analysis up to industrial pilot bioreactors or human bodies and bringing together in vivo, in vitro and in silico analysis methods of cellular systems.

The research focus on three key research lines: 1) explore the diversity and evolution of microbiomes and their functional potential for environmental applications, human and animal health; 2) design, engineer, and apply cell factories from a systems perspective; 3) build models that enable design, prediction, synthesis, and control of biological systems and their interactions at various levels.

The value of the theme's research is supported by the numerous publications in scientific journals contributing to the fields of microbial, microalgal and animal engineering, system health, environmental and human toxicology, food safety, novel testing strategies, microbial evolution, physiology, and molecular ecology. 25% of the publications from the theme are in the top-10% of global citations and the Field Weighted Citation Impact is 2.22, which is over two times the world average. Scientific excellence, as well as societal impact is exemplified by many of the research lines. Among those feature the advances in genome editing in diverse cell models (microbes as well as human cell lines) by CRISPR-Cas nucleases (see Case 1) and the impact of microbial communities (microbiomes), for instance, in the human and animal guts, as well as marine and other environments.

The viability is ensured by the acquisition of a large number of national (NWO, NWA-ORC, ZonMW, FOM) and international (H2020, Marie Curie, ERA, ERC Consolidator and Advance) grants awarded to personal and collaborative enterprises. Noteworthy is the awarding of both the Spinoza Prize and ERC-Advanced Grant (both worth €2.5 million) to Prof. John van der Oost in 2018 and 2019.

Of note is also the involvement of the theme in establishing the Wageningen Microbiome Center and the UNLOCK national infrastructure. Both operations place the theme into a leading position in the study of human-host interactions as well as allowing the groups to perform their research using cutting edge facilities.

In addition, the theme maintains close and fruitful collaborations with industrial partners, among others BASF, DSM, Corbion, Shell, Concawe, MSD, Nutricia and Unilever. These partnerships attempt to translate the scientific knowledge generated by the theme's research into real-world applications. Results of such effort are the high number of patents (>30) submitted in the last 6 years.

The theme aims at meeting clear societal needs in the areas of health and food, environmental sustainability, and clean biotechnical production of chemicals and fuels, and at engaging the public with the progress made via workshops, public lectures, appearances in radio and tv programmes among others. The theme is also very interested in making its results open to the public by publishing in open access journals, and by sharing data and developed software in a FAIR (findable, accessible, interoperable, reusable) manner to increase dissemination of its research.

Education together with personal development of students and young scientists is a key aspect for the success of the theme. Ample attention is given to good quality supervision and research for PhDs students. There are several career trajectories and possibilities for growth for staff members within and outside the theme.

Overall, all chairs offer an attractive, positive and collaborative environment that empower the development of scientists and grant them opportunity of success. Investing on excellence of the stakeholders within the theme place this VLAG theme in a strong position for additional acquisition of competitive research funding and for performing cutting-edge research that will leads to important fundamental discoveries and technological applications in the next 6 years.