7. Public Summary

In comparison to the previous evaluation in 2017, the Groningen Biomolecular Sciences and Biotechnology Institute has significantly strengthened its position during the assessment period of 2017-2022, despite facing challenges posed by the Covid-19 pandemic. During this period, we have demonstrated remarkable dynamism in terms of our staff members and diversity.

The majority of our staff members play prominent roles in national and international research programs, have secured substantial multi-million euros research grants, received awards and accolades, and actively participated in influential strategic committees that shape the future of chemistry and biology in the Netherlands and beyond. We have strengthened our interdisciplinary endeavors through activities through local, national and international programs, and have actively engaged in and contributed to public-private partnership programs.

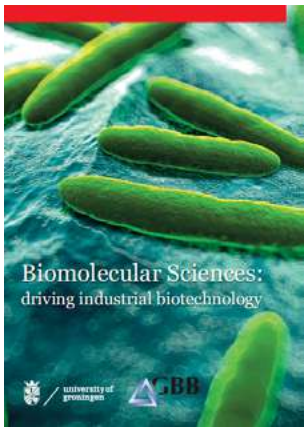
To reinforce our commitment to our two research domains Molecular Mechanisms of Biological Processes and Physiology and Systems Biology, we have successfully incorporated new research lines and appointed successors to retiring staff members, who have already established competitive groups. While our primary aim remains the pursuit of curiosity-driven fundamental research, we also actively engage with stakeholders who can translate our scientific breakthroughs into practical applications.

Our knowledge and patents have been utilized through the establishment of four start-ups, with GBB staff members serving as co-founders. We also actively enhance and strengthen our internal policies and processes to support our staff and early career researchers.

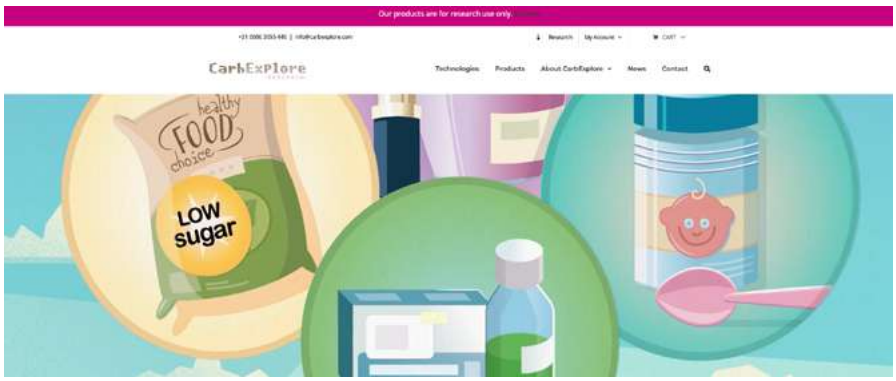
Our commitment to increasing impact of our work has resulted in publication of a growing number of scientific highlights that cater to professionals and the general public, while maintaining a consistent number of patent applications. The institute consistently attracts a steady influx of new bachelor's, master's, and PhD students, as well as postdocs each year. These individuals benefit from a comprehensive blend of theoretical and hands-on training in biomolecular sciences, nurturing their professional skills and empowering them to pursue careers in academia and industry, eventually assuming leadership positions.

Throughout the report, we outline our scientific breakthroughs and showcase selected achievements, referred to as showcases, which highlight our quality, viability, and societal relevance. These examples vividly illustrate our activities, coherence, successes, and impact. Overall, we firmly believe that we provide a solid foundation for strengthening our efforts in the upcoming period. In fact, the achievements of 2023 are already highly promising and will continue to evolve.

SHOW CASE 1
Societal Impact – Start-up companies originating from GBB

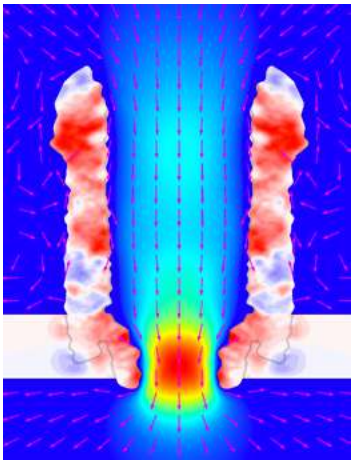


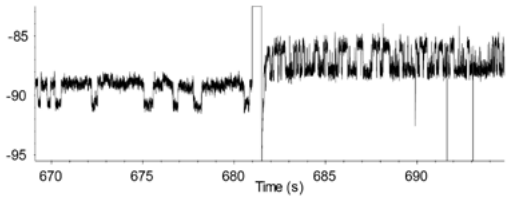
The excellent contacts and fruitful collaborations with SMEs and industry demonstrate GBB's strong societal relevance of the scientific breakthroughs achieved at the earliest stages of the innovation pipeline (see also Section 5.5). This success builds on the deep fundamental molecular knowledge that our private partners need to develop their production platforms or to design and validate their lead compounds (e.g., in drug development). Over the past period over 17 M€ has been attracted for precompetitive fundamental research led by GBB PIs, contributing with their expertise and in-house developed (platform) technologies. The established platforms still aid in progressing towards new molecular insights, but on their own are less scientifically challenging; nonetheless, they have potential to be exploited as commercial technologies.



From GBB two start-ups have emerged, each exploiting expertise and platform technologies for enzyme (re)design, activity screening, and protein/product production that originally have been developed and established at GBB. In the field of carbohydrate research, building on extended collaborations with industry via the Carbohydrate Competence Centre, the start-up **CarbExplore BV** was established in 2018. As co-founder, Lubbert Dijkhuizen (former head Microbial Physiology and retired in 2018) and several former GBB researchers continued with developing and producing carbohydrate active enzymes as well as synthesizing probiotic and functional carbohydrates for clients. CarbExplore is fully independent, is housed at one of the Innovation Labs at the Zernike campus, and currently has 12 employees. They provide services to major industries in Europe and the US in the area of food and nutrition, including the potato corporation Avebe that also has its research laboraties at the Zernike campus.

The FRESCO platform for enzyme engineering and screening established by Profs. Dick Janssen and Marco Fraaije has been instrumental for developing and redesigning enzymes with improved or novel activities. This approach also appeared of high interest to embark on collaborations in public-private partnership programs; however, such a platform also requires extensive effort to keep it running, which goes at the expense of fundamental and curiosity-driven research. Therefore, the second platform technology-based start-up **Gecco Biotech** was established in 2018 by a postdoctoral researcher (Dr. N. Loncar) and Marco Fraaije (head Molecular Enzymology). Gecco Biotech provides (analytical) services for enzyme development to public and private parties. During its early years Gecco Biotech is facilitated by GBB to operate within its premises. This allows the start-up to stay closely connected to new developments in research and to make use of the dedicated research infrastructure for providing their services, while simultaneously securing capital (mainly to invest in analytical equipment) to transition to an independent location, potentially at the Zernike campus. Gecco Biotech is fully independent and currently has 4 employees for executing their service analyses, mostly for private parties. Gecco Biotech also participates in many EU projects, often in conjunction with the research unit led by Prof. Marco Fraaije; this 'tandem' proves to be very beneficial for attracting external funds.





In contrast to the aforementioned start-ups, **Portal Biotech BV** (co-founders Giovanni Maglia and Bert Poolman) and the Dutch offspring of Portal Biotech Limited (UK) has been established in 2021 to further valorise IP generated at GBB (mainly the Maglia group) on engineered biological nanopores for developing i) (wearable) diagnostic devices to (remotely) sense biomolecules (e.g., glucose, protein, hormones, vitamins) and ii) novel miniaturized peptide sequencers that enable sequencing at the resolution of single peptides in mixed assemblies, including identification of post-translational modifications. The devices could resemble the Minion (Oxford Nanopore Techologies; see illustration bottom right) for solid-state pore-based DNA sequencing. At present Portal Biotech BV is licensee of 8 patents (with several upcoming) and has attracted initial investment funds for appointing up to 10 scientists. At present Portal Biotech is facilitated by using GBB premises, but in due time will move to its own location, potentially at the Zernike campus.

A fouth start-up, **Omnicin Therapeutics**, also plans to acquire a license on IP generated at GBB (Molecular Genetics), but currently is in a precompetitive stage to redefine its focus for agonistic use of metals and antimicrobial peptides.

SHOWCASE 2

Science with impact on Health – Structure-function relationships of disease-related membrane transporters

Every cell – from the simplest prokaryote to the most advanced eukaryote – is enclosed by a lipidic membrane, which is impermeable to most charged and bulky chemicals. To pass through this barrier, specific and diverse families of membrane-embedded proteins have evolved that allow the chemical influx into and efflux from cells in a highly regulated manner. The proper functioning of such an ensemble of transport systems is essential for cell viability and functioning. Ergo, malfunctioning of vital membrane transporters results in physiological disorders and (rare) diseases. Thus, by studying the transport proteins embedded in membranes, we can better understand the cell operation both at the microscopic level (e.g., substrate-binding, conformational changes, etc.) and at the macroscopic level (e.g., inter-cellular communication via signal transduction, cell response to the osmotic stress, etc.).

The GBB research groups Membrane Enzymology (Dirk Slotboom), Electron Microscopy (Cristina Paulino) and Biomolecular X-ray Crystallography (Albert Guskov), extended with molecular dynamics studies (Siewert-Jan Marrink), are investigating the transport mechanisms of various membrane transporters and their detailed structure-function relationships, also unraveling the molecular basis of the associated diseases. Their recent breakthroughs are:

- The detailed characterization of the transport cycle of Solute Carrier Family (SLC) 1 transporters (see illustration), where an ensemble of asymmetric states has been observed and the molecular mechanism preventing sodium spill has been revealed[1,2]. Mutation-caused abberations on chloride conductance during transport lead to a rare neurological condition known as episodic ataxia 6[1];
- The transport mechanism of the neutral amino acid exchanger ASCT2, linked to numerous cancers, has been characterized[4,5];
- The molecular determinants of spastic tetraplegia, thin corpuscallosum, and progressive micro-cephaly – together denoted as SPATCCM disease) caused by single mutations in ASCT1 transporters – have been described[6];
- The discovery of an ABC importer with the exporter fold, responsible for scavenging of vitamin B12 in Mycobacterium tuberculosis[7], as well as the discovery of a unique BtuM protein combining transport and enzymatic function of cobalamin decyanation[8]. These transporters are being evaluated as potential targets for novel antibiotics;
- The detailed functional and structural characterization of a unique toppling transport mechanism by ECF transporters[9-11] for obtaining mechanistic insights to understand development of neuro-degenerative diseases and how to treat these. On top of that, the researchers have developed the toolkit of photo-switchable and photocaged compounds for time-resolved characterization of membrane transport[12].

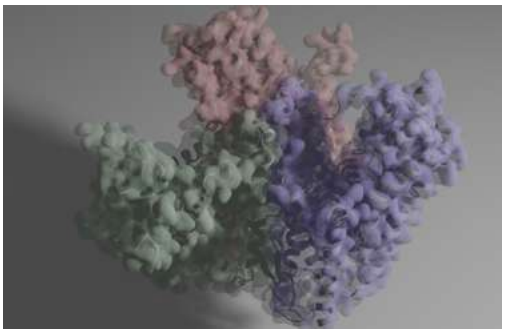


Illustration: *The membrane-embedded transporter GltTk as a representative of SLC1 family of transporters*

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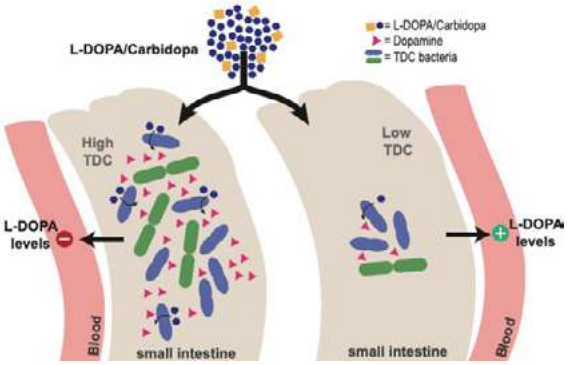
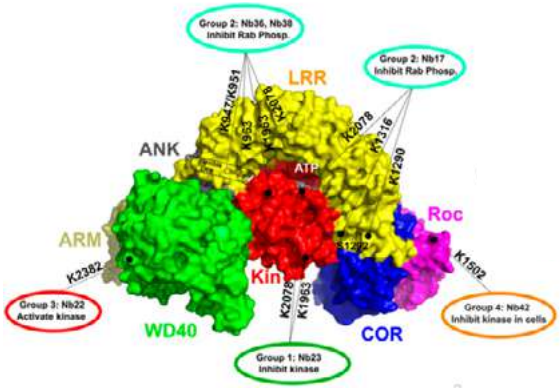
SHOWCASE 3

Science with impact on Health – Parkinson's disease: the search for the right cure

Currently in Europe there are over 1.2 million people living with Parkinson's disease and it is predicted that there may be nearly 13 million people suffering from this disease by 2040. As numbers are increasing, and there is no effective cure, novel treatment strategies are needed to help patients diagnosed with Parkinson's disease. Molecular studies at GBB aim to unravel fundamental insights of molecular mechanisms and investigate on how to interfere with or inhibit these mechanisms. The systems studied allow for the full functional analysis from molecular structure (e.g., RNA, (membrane) proteins) to organelles (e.g., peroxisomes) and cellular processes (including cell division, metabolism, host-microbe interactions, immunity, drug resistance) and provide the basis for explaining disease mechanisms. Our molecular knowledge on disease-related processes, generally published in top-ranked peer-reviewed journals, attracts substantial attention of SMEs, industry as well as private foundations. To exemplify this, we outline several major achievements of the last 6 years connected to biomolecular studies that should provide strategies to tackle development of Parkinson's disease.



The current gold-standard of Parkison's treatment involves the pharmacological replacement of dopamine via the systemic administration of levodopa (L-3,4- dihydroxyphenylalanine), a catecholamine (a large neutral amino acid) that instead of dopamine crosses the blood-brain barrier. In the brain, levodopa is metabolized to dopamine by the dopamine decarboxylase. The team of **Sahar El Aidy** has demonstrated that gut-associated bacteria, particularly *Enterococci*, harbor the tyrosine decarboxylase (TD) that efficiently metabolizes levodopa to dopamine[1]. However, this peripherically produced dopamine cannot cross the blood-brain barrier anymore. Thus, bacterial conversion of levodopa decreases the bioavailability of levopoda for treatment, necessitating patients to require higher and/or more frequent dosages of the medication[1-3]. By reliably measuring gut bacterial TD activity, clinicians can gain insights into developing new strategies for managing Parkinson's disease symptoms and improving treatment outcomes for patients. These scientific breakthroughs also prompted several precompetitive research projects with private parties, including among others OrionPharma and Stellate Therapeutics. This research led by Sahar El Aidy aimed on gaining detailed insights on lead compound metabolization by gut bacteria and subsequent further compound and product development by the company.



Mutations in Leucine-rich repeat kinase 2 (LRRK2) are so far the most frequent cause of late-onset and idiopathic Parkinson's disease and recent data suggest that, independent of mutations, increased LRKK2 kinase activity plays an essential role in the pathogenesis. **Arjan Kortholt** is member of the LRRK2 Function and Structure Consortium that has been consecutively supported by the MJ Fox Foundation since 2010. His lab has, in close collaboration with industry (Merck, GlaxoSmithKline), combined biochemistry with structural characterization to optimize LRRK2 kinase inhibitor binding[4,5]. Although, many LRRK2-specific brain-penetrant kinase inhibitors have been developed, most of them have major side effects, and none of the inhibitors can be used for the disease treatment yet. Therefore, targeting other domains of LRRK2 instead of the kinase domain has high potential for improved therapeutic benefits. Recently, high quality full-length LRRK2 has been purified to obtain the first structural map[6] for developing novel allosteric tools to target LRRK2 activity (see illustration). In collaboration with the labs of Profs. Versées (VUB, Brussels) and Gloeckner (DZNE Tübingen), a set of nanobodies have been generated that can modulate LRRK2 activity[7]. With the Kennedy lab (UGA, Athens) a set of stapled peptides have been designed that effectively disrupt LRRK2 dimerization and rescue LRRK2-mediated cell-death[8]. Currently, the Kortholt lab is working together with companies (e.g., Ambagon Therapeutics, Rappta Therapeutics, VectorY Therapeutics, LDC Dortmund) to further develop these and other compounds that allosterically regulate LRRK2 activity, with the goal to bring them into the clinic.

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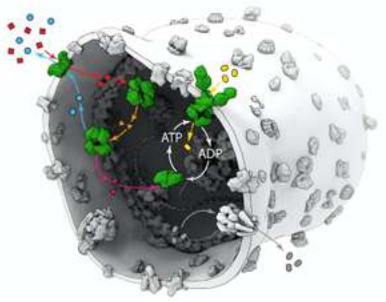
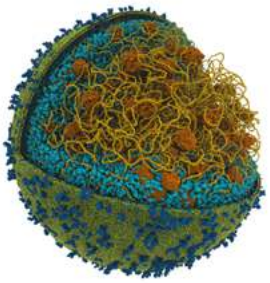
SHOWCASE 4
Science for science – Constructing synthetic cell-like systems

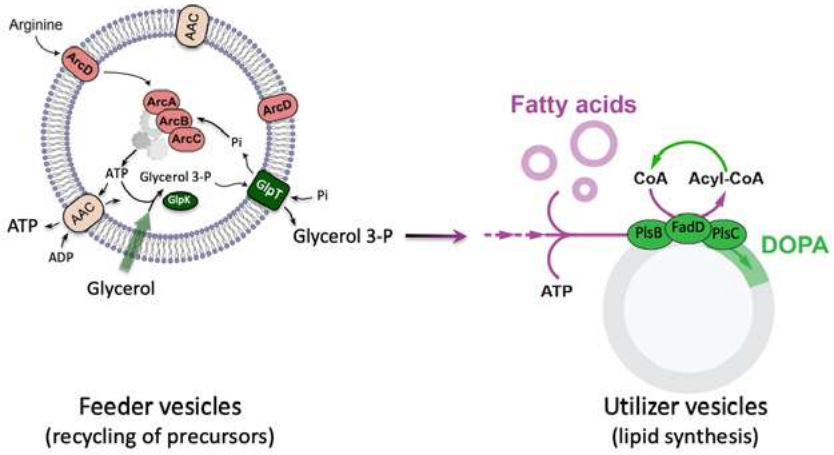
Living systems have the unique ability to self-organize, grow, replicate, and evolve through a continuous flow of energy and matter, a feature that has never been possible to recreate in man-made systems. In fact, a blueprint of building even the smallest and simplest living organism – bottom up from scratch – is lacking and is one of the most formidable and exciting challenges of the 21st century science and technology. In fact, minimal cell-like systems capable of autonomous, metabolism-driven growth and division will constitute powerful platforms that push current boundaries in biotechnology and will allow the future engineering of production systems as well as of (nano)materials with totally new functionality and full controllability.

The GBB research groups led by Matthias Heinemann (Molecular Systems Biology), Arnold Driessen (Molecular Microbiology), Siewert-Jan Marrink (Molecular Dynamics), Bert Poolman, and Dirk Slotboom (both Membrane Enzymology) form part of the Ducth gravitation program Building-a-Synthetic cell (BaSyc), which uses the *bottom-up approach to construct cell-like systems* from a minimal set of well-defined active elements (upper illustration at the right). They combine experiments, modeling and computer simulations to develop increasingly advanced metabolic networks to support biosynthesis for cell growth. They aim to understand life as an assembly of active modules and machineries with the remarkable ability of establishing and sustaining *spatiotemporal order away from thermodynamic equilibrium*, characterized by the concept of functional self-organization.



In the first five years of the BaSyc program, they have modeled an entire cell at full complexity, using the minimal cell JCVI-syn3A as starting point (lower illustration at the right). They have constructed selectively open cell-like containers with control of solute fluxes to feed an internal metabolic network and a constant supply of energy to fuel ATP-requiring processes, regenerate *redox cofactors*, and maintain *physicochemical homeostasis*. They also have developed ATP and proton motive force generating systems in vesicles that perform at least an order of magnitude better than synthetic vesicle systems described so far. The systems enable control of the volume, osmotic pressure, ionic strength and pH of the vesicles. Furthermore, they have developed functional mimics of mitochondria (generation of proton motive force, synthesis of ATP) and endoplasmic reticulum (lipid synthesis), and achieved *cross-feeding of precursors* between different populations of vesicles, and the synthesis of lipids for membrane growth (Illustration below).





Top illustration:
a schematic presentation of the bottom-up construction of the bioenergetics pathway.

Bottom illustration, right:
a complete cell model based on advanced coarse-grain molecular dynamics simulations.

Bottom illustration, left:
schematic presentation of a ATP and proton motive force generating system.

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SHOWCASE 5

Science – Towards robust biocatalysts by redesigning and resurrecting enzymes

Enzymes are nature's tools to make things happen, being molecular chemical factories, which catalyse a plethora of chemical reactions in biological systems and which have evolved to become extremely efficient in their task. Already for thousands of years, enzymes are exploited for human use, for example as components of yeast cells to allow beer brewing and for preparing bread. With the urgent call to address societal and sustainability challenges (e.g., fossil-to-biobased transition, chemical building blocks, biochemicals & pharmaceuticals, biofuels, functional food & nutrition, etc.), the interest in and need for bio-based solutions to solve societal challenges has rapidly increased and (engineered) enzymes (also referred to as biocatalysts) applied in sustainable biotechnology can and will provide unlimited solutions. Yet, often enzymes are required that should operate under extreme and unnatural conditions or should catalyse specific chemical reactions that do not exist in nature. Thus, there is a high demand for robust tailored enzymes, and for tuning such enzymes a detailed knowledge of their molecular functioning is needed combined with effective molecular tools to engineer them.

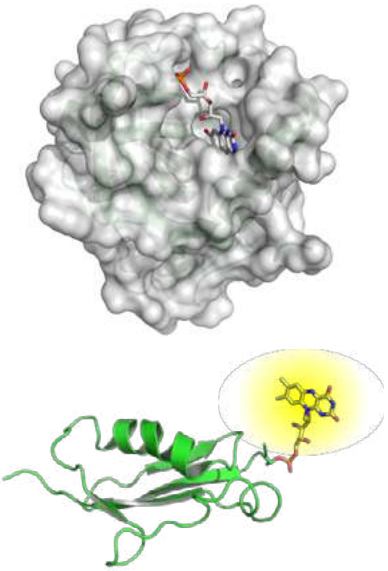

Illustration left:
A surface display of an engineered enzyme for the synthesis of the unnatural phosphorylated F0-cofactor.

Illustration right:
A model structure of a flavin-tagged protein.

The GBB research unit Biotransformation and Biocatalysis, with research groups being led by Dick Janssen, Marco Fraaije, and Max Fürst, focuses on studying the function of enzymes at the molecular level, combining biochemistry and structural biology. Their knowledge forms a strong basis for developing and employing new methods for redesigning and engineering enzymes. The enzyme redesign is supported by computational analyses and predictions, and experimental methodologies are targeted at effective production and smart screening of focused libraries of enzyme variants. In recent years, the approach of enzyme engineering also includes newly developed approaches to resurrect ancestral enzymes. The group has been very successful in identifying and tuning enzymes for industrial applications, such as various transaminases (for pharmaceuticals), oxidases (for biomass valorization), monooxygenases (for pharmaceuticals and chemical building blocks) and peroxidases (for biosensing). Together, these research activities have yielded:

- Knowledge-based discovery of new enzymes, such as the first discovered HMF oxidase and several F420-dependent enzymes [1,2];
- New insights into mechanism and structure of enzymes, such as the first elucidation of mammalian flavin-containing mono oxygenases[3-5];
- Development and successful implementation of computational protocols to guide enzyme engineering, such as the effective FRESCO protocol that assists in predicting mutation to render enzymes thermostable[6-8];
- Design of new cofactors, cofactor recycling approaches and cofactor-based protein labelling methods[9,10];
- Resurrection of ancestral cofactor-dependent enzymes, leading a better understanding of enzyme evolution and function[11,12].

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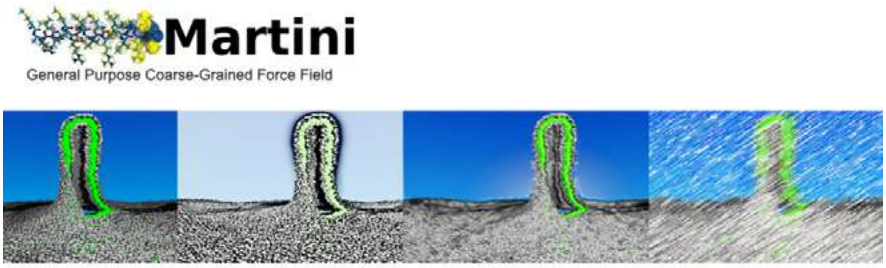
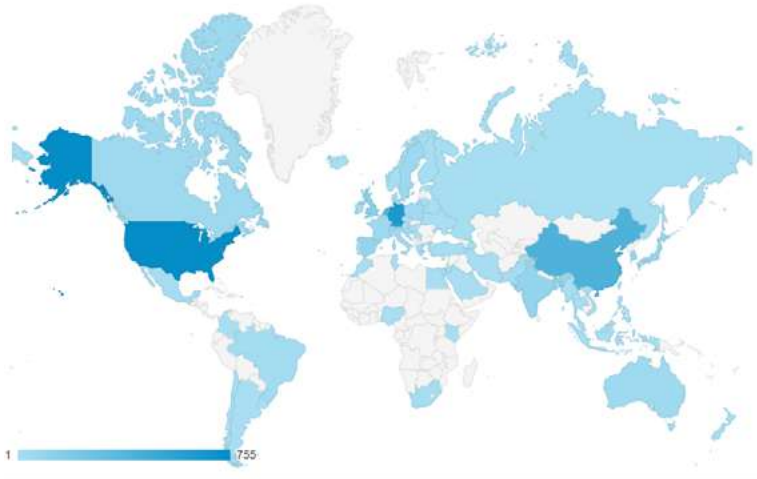
SHOWCASE 6
Societal Impact – Computational tools for (precompetitive) science

The genomics revolution coincided with the need for unravelling meaningful information from massive datasets and more importantly to integrate genome-level data such as single-nucleotide polymorphisms, transcriptomes, metabolomes, proteomes, secretomes, lipidomes, etc.; collectively defined as '*omics*'. In parallel, theoretical and computational methods were developed for modelling and simulating molecular interactions, which nowadays have resulted in advanced tools such as Alphafold and MARTINI. Advanced computational tools are of utmost importance for scientists in academia and industry as they aid in understanding of experimental data or, *vice versa*, unravel hidden or unexpected insights that prompt new studies or strategies for product development (drugs, enzymes, proteins, etc.). At GBB cutting-edge computational tools are firmly integrated in education and research. Moreover, several groups are very active in developing such tools. Extending these tools with machine learning and artificial intelligence approaches also is foreseen, for instance, to (re)design enzymes (e.g., Max Fürst), to unravel structural dynamics of RNA (e.g., Danny Incarnato), and to allow high-throughput molecular dynamics simulations (Siewert-Jan Marrink). Several in-house developed computational tools have found their use worldwide and clearly are much appreciated by users and a few are exemplified:



The first concerns CG MARTINI, which is a dedicated computational platform for coarse grained molecular dynamics simulations that allow analysis of mechanisms and processes from molecules to organelles with the vision to simulate entire cells. MARTINI has developed rapidly as open source in the last decade and in 2021 MARTINI 3 was launched (*Nature Methods* 18) as a general-purpose force field for coarse-grained molecular dynamics. The developments of MARTINI, led by Siewert-Jan Marrink (Molecular Dynamics), progresses simultaneously with its application for answering scientific questions. For the latter, many collaborations exist within GBB, locally at FSE, but also with prominent researchers outside the university and the Netherlands and including those who study advanced materials instead of proteins, lipids or biological processes. At present, CG MARTINI has >4,630 registered users worldwide, who can request for technical support that is provided by the researchers in Marrink's group.



Bioinformatics is essential to draw meaningful omics-based conclusions. At Molecular Genetics several highly relevant tools have been developed under the guidance of Profs. Oscar Kuipers, Jan Kok, and Dr. Anne de Jong that are used extensively worldwide. Excellent examples are i) BAGEL (4th version published in Nucleic Acid Research 46, 2018) with >500,000 searches, which has received >1,000 citations for mining bacterial (meta)genomic DNA for bacteriocins and RiPPs, and ii) the newest AI-based tool FUNAGE-Pro provides a comprehensive web server for gene enrichment analysis of prokaryotes, enabling the identification of overrepresented functional classes in sets of genes and proteins and allowing uncovering of biological functions from differential gene/protein expression studies, for any bacterial genome and for multiple types of experiments, time series, clusters and networks. Although its precessor was not officially published (but has been used >1 million times!), FUNAGE-Pro was published in July 2022 (Nucleic Acid Research 50), already has thousands of users and searches worldwide (see illustration) and is expected to be used frequently by scientists in both academia and industry and students (e.g., in bioinformatics and AI).