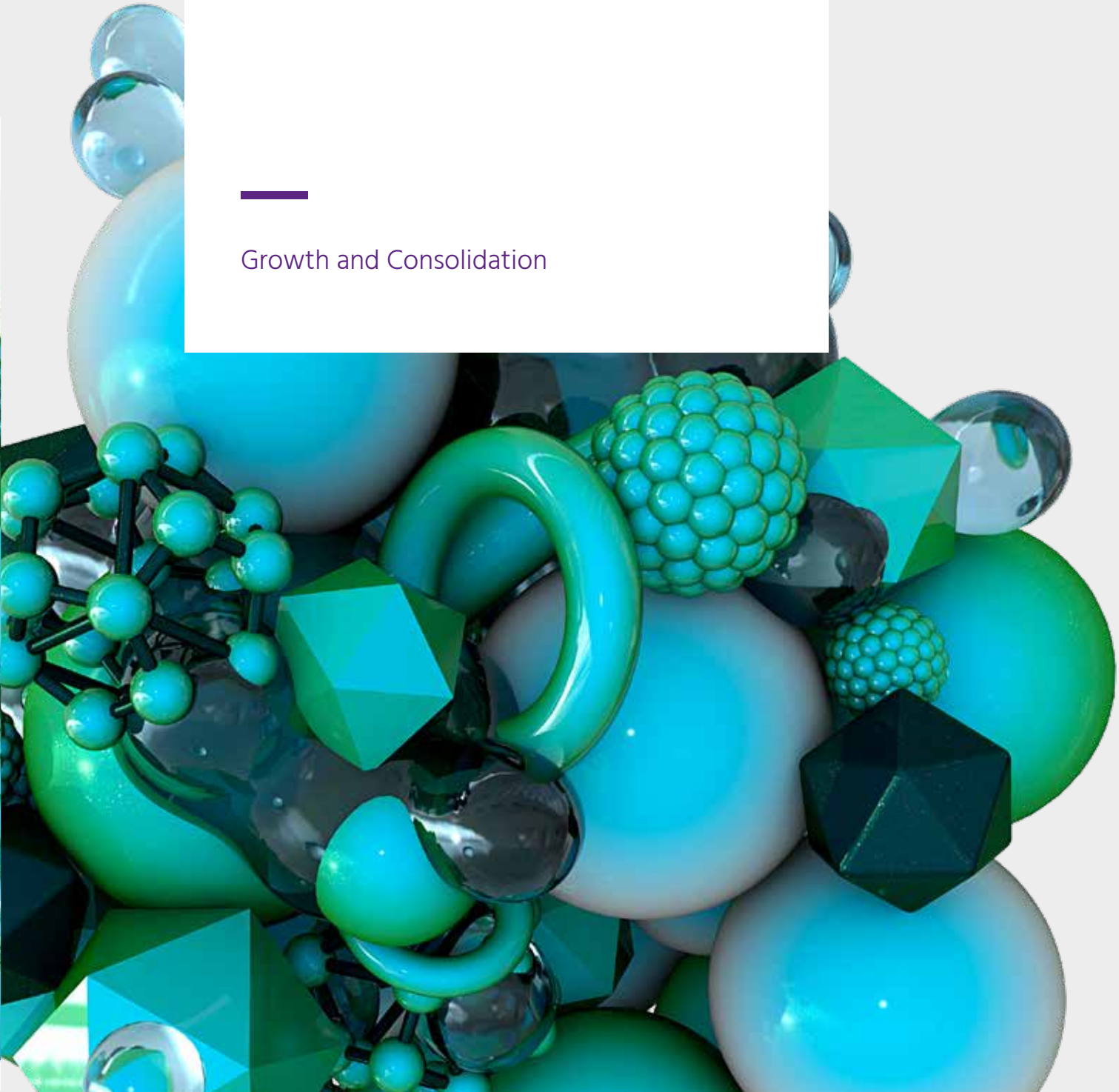
CENTRE FOR DIGITAL LIFE NORWAY

ANNUAL REPORT 2017

Growth and Consolidation



«KNOWN RESOURCES –
UNDREAMED POSSIBILITIES»

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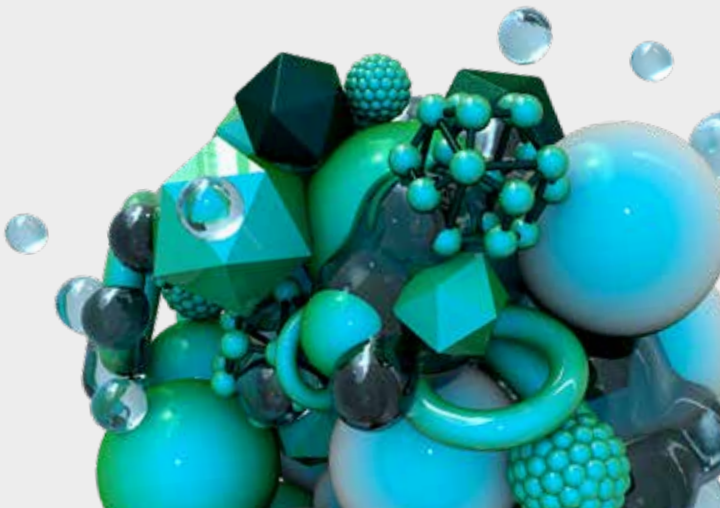


FROM THE CENTRE LEADER

Dear all!

Centre for Digital Life Norway (DLN) has been running for 2 years! In this second year, 6 new digital life research projects were initiated and 8 partner projects became affiliated with DLN, substantially increasing its size and impact. Most of all, DLN is about excellent transdisciplinary science executed in these diverse research projects. In parallel, the DLN core areas; data & infrastructure, innovation and industry involvement, responsible research and innovation (RRI), and researcher training, have been developed in fruitful collaboration between the network project and the research projects, and in open interaction with remaining scientific community. DLN is strongly anchored into the host (NTNU, UiO, UiB) and partner (NMBU, UiT, Sintef) institutions and the centre has rapidly become an important trans-national player in changing and shaping the Norwegian Biotechnology landscape. DLN represents a strong and collaborate national voice in strategic decisions; all of this in agreement with the vision and ambitions of establishing this Centre. DLN has become a novel and internationally recognized platform for integrated biotechnology and RRI, putting a new dimension into the transdisciplinary nature of the centre.

In late November 2016 the Norwegian Government released its bio-economy strategy; "known resources – undreamed possibilities." This strategy aims for a better and sustainable exploitation of our renewable biological resources. In this important document, capacity building and investments in research and innovation are regarded prerequisites for success. Moreover, collaboration across the disciplines and geography through network clusters, research centres and international focus, are highlighted. These goals and ambitions are very much in agreement with the DLN vision, and our Centre should represent one important contributor to implementing the bio-economy strategy.

We truly experience that there is a national need for the DLN core activities, and in particular, DLN has strong emphasis promoting and building culture for more innovation in digital biotechnology, together with existing central players in Norway. The DLN Network project has the competence, the continuation and resources, and the long-term perspectives needed to be successful in promoting more societal, economic and environmental value creation out of the biotechnology research in Norway.

We are looking very much forward to the continuation together with all of you in 2018!

Trygve Brautaset, Centre leader

COMMENTS FROM THE BOARD CHAIR

I think it will be clear to all readers of this second annual report that time has been used well since Digital Life Norway (DLN) was established two years ago. DLN provides a novel organizational framework for biotechnology research in Norway. The centre is as a joint venture between the three hub universities, NTNU, University of Bergen and University of Oslo, which all are represented on the board. In addition, node institutions, defined as all institutions with DLN-funded research projects (currently SINTEF and NMBU), hold two seats on the board and external industry representatives hold two seats. The hub and node institutions are competitors in the Norwegian landscape for research funding, researchers and students, so building an effective national team for biotechnology research and training is a long-term project. Fittingly, year one was dedicated to trust and year two has been dedicated to consolidation and growth.

To the board, it is clear that DLN is developing according to plan. Whereas the DLN management is responsible for daily operations and initiating the various activities in DLN, it is my humble opinion that good discussions and solid input from all board representatives has contributed to shaping the direction and collaborative atmosphere of DLN. Additionally, the mere existence of DLN has provided the major universities in Norway with a venue for dialog and consensus building for how to approach research, innovation and training within the biotechnology domain. Two examples of this are the suggestions for the next Digital Life call in Biotek-2021 that DLN has sent to the Research Council of Norway (RCN) and the joint response to the RCN strategy related to infrastructure for biotechnology.

The task of DLN is to not only support high-quality research and make Norwegian biotechnology research more interdisciplinary, but also to build a national platform for innovation from biotechnology. Whereas research institutions have all the necessary disciplines for the former, the latter challenges us to reach out to other actors in the ecosystem for innovation. There is a demand from society that universities and research institutions contribute more to innovation, but exactly what should be our role in an innovation pipeline is still a matter of debate. It is a major focus of DLN to address this issue. Taking stewardship of innovation in Norwegian biotechnology is a daunting task that DLN cannot do alone. Thus, DLN needs to reach out to industry and provide the right incentives for industry to engage with academic researchers. I am looking forward to seeing how the DLN management will address this issue in the years to come and as a board member I hope to be able to play a small part in all of this.

Finn-Eirik Johansen, Chairman of the board

ONE VIRTUAL CENTRE

Centre for Digital Life Norway (DLN) is a virtual centre, institutionally anchored at NTNU, UiO and UiB. It is funded by the Research Council of Norway under the Digital Life (DL) initiative and receives in kind support from the host universities. The centre is built around the 12 research projects are currently funded through the research council's Digital Life initiative. DLNs mission is to build capacities for disciplinary convergence in digital biotechnology through education and training, to strengthen shared digital infrastructures, to leverage innovation and industrial partnerships, and to foster social responsibility. The following illustrates some of the centre's many networking activities during 2017, most of which adressed a need in one or more of the centre's research projects.

DigitalLife is the annual conference of the centre. This year is was held in Oslo and gathered scientists interested in digital biotechnology for inspiring talks from members of the DLN Scientific Advisory Board, DLN project managers, and, last but certainly not least, brilliant young researchers. Talks from this conference can be found on the YouTube channel Digital Life Norway.

The Digital Life research school is a core component of the virtual centre and admits PhD students and postdocs working in digital biotechnology in Norway, irrespective of their affiliation to a Digital Life funded research project. In 2017, the school offered a portfolio of technical courses as well as training in transferable skills that 106 young researchers attended. The school provided travel grants to 52 members to attend 15 different out of town workshops or summer schools. Additionally, the first annual meeting of the research school was held. By year's end, enrolment grew to 150 members, spread across the partner universities in Trondheim, Oslo, Bergen, Tromsø, Stavanger, and Ås.

Important steps have been taken in 2017 on concretising two additional programs to promote career development in digital biotechnology. Firstly, five promising young researchers were selected on a competitive basis to join the Digital Life Excellence programme, which supports them in selecting an international mentor and prepare an application for a prestigious grant within digital biotechnology. A new call for five more candidates will be announced in 2018. Secondly, preparation for an industrial internship for early career researchers started in 2017, with a pilot run scheduled for 2018.

What are the opportunities for digital biotechnology to foster growth in the Norwegian bioeconomy? Unveiled on March 21st to an audience of 250 people attending the Digital Life Innovation Day in Oslo, the report "Den digital bioteknologien I Norge"[1] aims to answer this question. It shows that companies and R&D organisations have a substantial interest in digitial biotechnology, which they hope to enable shorter product development timespans at lower cost. The report further diagnoses substantial interest in developing closer relationships between businesses and universities, which is a domain that DLN is actively promoting.

Immaterial property rights (IPR) are a key instrument in creating economic value from research. How can we ensure that we capture and exploit ideas? How can we develop collaboration between academia and business? In November, DLN arranged a seminar on IPR in collaboration with Foods of Norway (NMBU), SINTEF, Inven2, Innovation Norway and Onsagers.

Staying with questions at the heart of digital biotechnology, can all aspects of life be simulated in a computer or are there properties of living systems that elude mathematical modeling? During the workshop 'modeling living systems' these issues were discussed in general as well as for the different modeling approaches that the participants presented. They were given the task to identify possible obstacles that would limit the predictive power of their models in a pure scientific setting as well as in the setting of their extended applications. The workshop explicitly curated a stimulating debate about the social and environmental responsibilities inherent in scientific modeling, i.e. when seemingly innocent model assumptions come to underpin policy decision.

«BY YEAR'S END, ENROLMENT GREW TO 150 MEMBERS, SPREAD ACROSS THE PARTNER UNIVERSITIES IN TRONDHEIM, OSLO, BERGEN, TROMSØ, STAVANGER, AND ÅS»

Modeling was also the topic of the 2017 'Methodologies for Digital Life' meeting. It focused on metabolic systems, which is a core topic in many Digital Life projects. Keynote speaker Bernhard Ø. Palsson from the University of California San Diego delivered a Volterra lecture[2] on the topic of global scale metabolic models. Palsson is a pioneer in this field. In his talk he not only presented how these models work, but also laid out paths towards understanding adaptation and regulation of metabolism. Several Digital Life research projects make use of this modelling approach (also called constraint-based modelling, CBM), which creates potential synergies between the projects. In a complementary talk Peter Ruoff (UiS) talked about his collaboration with control engineers and how they apply control theoretical analysis to understand how control of biological processes arise from the mechanistic level of molecular kinetics.

In August, Francis Doyle visited the Artificial Pancreas Trondheim (APT) project and gave his Volterra lecture entitled "A Systems Approach to Treating Diabetes". Prof Doyle is a scholar in chemical engineering and currently the Dean of John A. Paulson School of Engineering and Applied Sciences (SEAS) at Harvard University. His research group pursues the development of optimal automated blood sugar control as a way to effectively curing type 1 diabetes mellitus (T1DM). His team has chosen a systems engineering approach, combining the fields of systems biology and functional biomedical control.

PARTNER PROJECTS

DLN is an open an inclusive centre for communities working on digital biotechnology. There are two ways to join the centre: projects funded under the Digitial Life initiative become members by default; projects financed from other sources may apply for membership, provided they have a digital biotechnology profile. This year the following eight projects were granted membership as partner projects in the centre:

- AHA! - Adapted Heuristics and Architecture: Towards an understanding of personalities and phenotypic diversity. Project leader: Jarl Giske, UiB
- Chartering Chemical Space of Riboswitch Ligands - Towards Future Antibiotics. Project leader: Ruth Brenk, UiB
- Elucidation of biological nanoparticle formation mechanisms. Project leader: Dirk Linke, UiO
- DrugLogics – Rational development of anti-cancer drug combinations. Project leader: Astrid Lægreid, NTNU
- ParkOme – Mechanisms, disease markers and treatment targets for Parkinsons Disease through systems and network biology. Project leader: Charalampos Tzoulis, UiB
- PerCaThe – Personalised Cancer Therapy. Project leaders: Kjetil Tasken/Arnoldo Frigessi, UiO
- Big Insight (SFI) – Innovative solutions for key data-driven challenges. Project leader: Arnoldo Frigessi, UiO
- CCBIO (SFF) – Centre for Cancer Biomarkers. Project leader: Lars A. Akslen, UiB

[1] The centre would like to thank the Bio-economy reference group for their contribution to the report.
[2] Vito Volterra was a pioneer in applying mathematics and physics to biology as early as the 1900; the high profile lecture series in Digital Life is named in his honor.

DATA MANAGEMENT IN DLN

Emerging technologies continue to make biology more and more data intensive. In addition, biotechnological research projects now often rely on collaborations between researchers with different competences. These emerging challenges put a higher demand on good ways of sharing data in research projects and of standardizing and documenting how they were created and analyzed.

DLN supports and promotes the use of data management and the centre arrange training workshops and collaborate with data management resources to improve and develop tools for data management in life sciences. During the hands-on training workshop in May, we had trainers from the FAIRDOM association in Manchester and Heidelberg, teaching data and model management in the data management software SEEK. In addition, trainers from ELIXIR Norway gave an introduction to the Norwegian e-Infrastructure for Life Sciences (NeLS). New training options are under planning for 2018.

IMPROVING TOOLS FOR DATA MANAGEMENT IN LIFE SCIENCE

Many of our research projects are using or planning to use the SEEK platform. To improve access to national infrastructure for data storage and to provide better analysis and documentation of omics data, DLN is supporting an integration work between SEEK and NeLS. Data residing in NeLS can be easily shared between national project participants and will have access to long-term storage through ELIXIR services with the NIRD (National Infrastructure for Research Data) infrastructure of UNINETT Sigma2. By connecting NeLS and SEEK, users of both resources get access to a whole new set of tools. This will improve the organization of data, metadata, protocols and analysis (models), it will allow using and building of bioinformatics analysis pipelines through the NeLS Galaxy workbench as well as improved data storage capabilities.

We are now collaborating with several DLN projects (DigiSal, dCod 1.0, INBioPharm and BioZEment) to test new features of NeLS/SEEK. After testing and appropriate modifications the new versions of NeLS and SEEK will be made available to all users – hopefully during the spring of 2018.

Lunch by the sea at the Hands-on workshop on data management

FAIR DATA MANAGEMENT

The FAIR principles are a set of best practices to make scientific data, analysis of the data, pipelines etc. better suitable for sharing and reuse in the scientific community. FAIR stands for Findable, Accessible, Interoperable and Re-usable. More information about how to make your science FAIR can be found at the Force11[1] site and in Wilkinson et al[2].

FAIRDOM[3] AND SEEK

SEEK, is a web-based resource platform for managing and sharing heterogeneous scientific research datasets and models in projects inside FAIRDOMHub, but it can also be installed locally. SEEK is based on the ISA format; Investigation, Study, Assay and is flexible in terms of the type of data stored. The metadata or smaller derived data sets can be sorted in SEEK while pointing to the local data storage. SEEK also provides tools to implement standards in for simulation and analysis of biochemical reactions and networks and Rightfield, a tool for annotating spread sheets to create semantically aware Excel spreadsheet templates.

ELIXIR NORWAY AND NELS

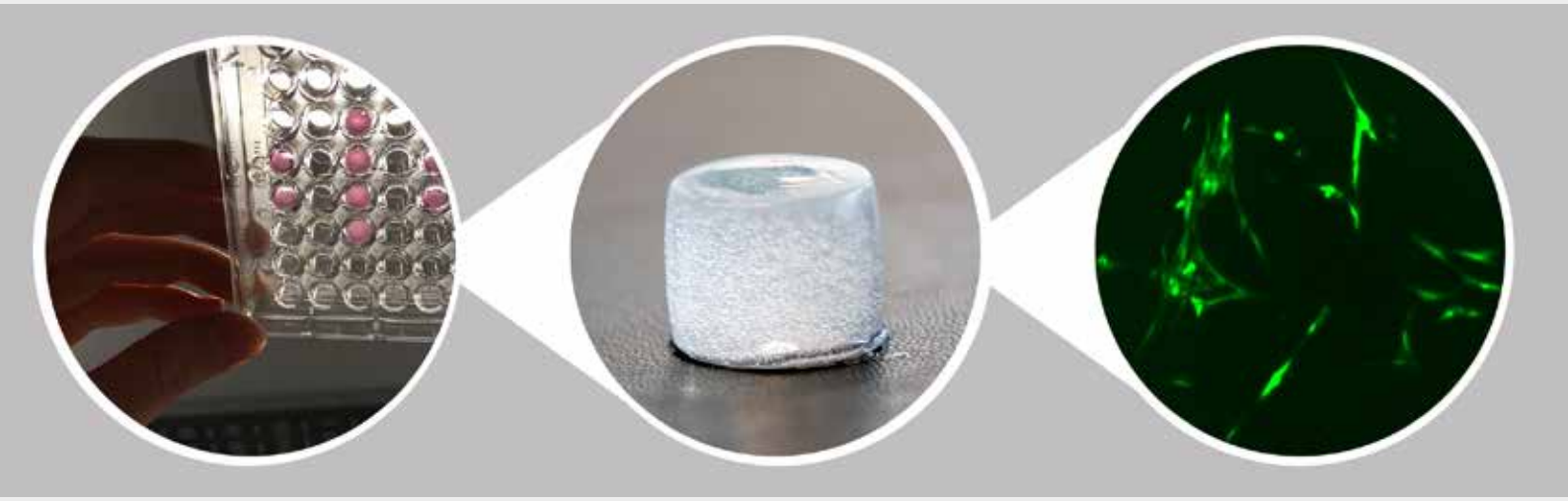
NeLS[4] (Norwegian e-infrastructure for Life Sciences) developed and supported by ELIXIR Norway, is an infrastructure providing storage, data sharing and analysis tools. NeLS connects to the national data storage platform NIRD, allowing long-term storage. For data analysis and computing, Galaxy is used in NeLS. Galaxy is an open, web-based platform for accessible, reproducible, and transparent computational biological research that allows computational workflows to be set up and used without the need of programming skills.

[1] www.force11.org
[2] doi:10.1038/sdata.2016.18
[3] www.fair-dom.org
[4] https://nels.bioinfo.no

3DLIFE – EMULATING LIFE IN 3D WITH DIGITAL AND EXPERIMENTAL TISSUE MODELS

Cell culture-based experiments are important pillars in all medically related research, allowing examination of living cells without the use of research animals or human subjects. However, the commonly used cellular monolayer cultures are a remote reflection of in vivo conditions, due to a lack of the cellular, structural and chemical elements forming the tissue microenvironment. This disparity results in cells losing their tissue-like phenotype over time, limiting the potential of the models for studying tissue biology and disease progression, and for testing pharmaceutic and toxic compounds.

3DLife aims to develop novel strategies for microtissue engineering in 3D, to provide model systems of organ function and bridge the gap to in vivo conditions. We take a bottom-up approach by using alginate, a seaweed derived polysaccharide, as a basis for hydrogels as tissue constructs. We have started the project with the grafting of biological signals on the biologically inert alginate. The mechanical properties of the hydrogels were further tailored within a range that has been shown previously to be relevant for soft tissue. Further, we have cultured fibroblasts in the hydrogel structures, showing good viability. These are important first steps to make tissue constructs. Importantly, although all partners are not yet experimentally active in the project, all have participated in the detailed planning of the initial experiments and protocols. This, together with spending time on protocol optimization, limits the numbers of possible pitfalls later in the project and makes all partners aware of experimental challenges. We started also initial RRI work on reflections in our kick-off meeting and with our RRI PhD student that has been following our work in the lab to get a clear understanding of the project, and also the investigators. Our ambition in the first part of the project is to understand and tailor the mechanical and biological properties for maintaining fibroblast phenotype in the tissue constructs. Furthermore, we will build up a library of alginate-based materials as well as a robotic screening system relevant also for other cell types than fibroblasts. By extracting RNA data from the cells, we will detail the cell analyses as well as develop computational models that can predict and interpret how cells are affected by artificial tissue environments. This will ultimately be applicable to a broad range of in vitro studies as well as optimization of tissue engineering scaffolds for clinical implementation.

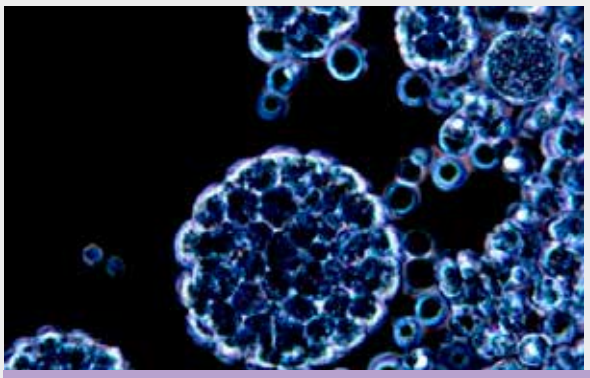


AurOmega – microbial production of omega-3 fatty acids

A joint NTNU and SINTEF project to establish a knowledge platform on DHA synthesis and lipid accumulation in the native DHA-producing thraustochytrids, and to develop these into high productivity omega-3 fatty acid producing cell factories.

The long-chain omega-3 fatty acids EPA and DHA are essential for humans, as well as for marine fish species. The current source is fish oil. As wild fish catches cannot be further increased, continued growth of marine aquaculture, in Norway and globally, is now seriously constrained by the availability of fish oil. New, sustainable sources of EPA and DHA are needed. Thraustochytrids are unicellular eukaryotic microorganisms, able to accumulate high levels of lipids. They can be cultivated at high cell concentration and are extremely promising organisms for development of economic competitive production processes for omega-3 fatty acids. Despite many years of research, there is still a lack of basic understanding of fatty acid synthesis in thraustochytrids, where DHA and saturated fatty acids are produced by two competing pathways. AurOmega partners NTNU and SINTEF have over the last decade isolated a high number of thraustochytrid strains and characterized their lipid-producing potential. The systems biology approach in AurOmega will provide an enhanced understanding of what limits the DHA synthesis in thraustochytrids and how it can be improved. An iterative approach applying high integration of experimental disciplines, with extensive omics analyses and mathematical modelling will be used. The mathematical and computational analysis will be based on genome-scale metabolic reconstruction and simulations to predict metabolic performance profiles, and complex network analysis to identify key regulatory features of DHA-synthesis, with particular focus of increasing the rate of DHA-synthesis and introduction into the storage lipids. The acquired new knowledge will be translated into enhanced DHA production capabilities of selected thraustochytrid strains. This will form the basis for a sustainable and economically feasible industrial omega-3 fatty acid production process, thereby enabling further growth of one of the most important industries in Norway.

The AurOmega project started 1st Oct 2017 and is still in the phase of recruiting personnel. Full activity is expected from second quarter 2018. The first year with establishment of metabolic model, tools for strain engineering and high resolution cultivation with deep phenotype analysis will form the basis for advanced experimentation in the later stages of the project.



Thraustochytrids grow as individual cells but easily flocculate at later stages of the cultivation.

The picture to the right shows centrifuged thraustochytrid biomass after a pilot scale cultivation for preparation of biomass to fish feed trials. The red colour origins from a minor production of carotenoids in addition to the large intracellular accumulation of lipids with a high content of DHA.

BioZEment 2.0 – a sustainable alternative to conventional concrete

The production of concrete accounts for more than 5% of global anthropogenic CO2 emissions. The BioZEment project aims to develop a more sustainable alternative to conventional concrete through the use of naturally occurring mineral-microbe interactions, by integrating efforts across multiple disciplines, including biotechnology, nanotechnology, geochemistry, techno-economics, and social sciences.

AMBITIONS

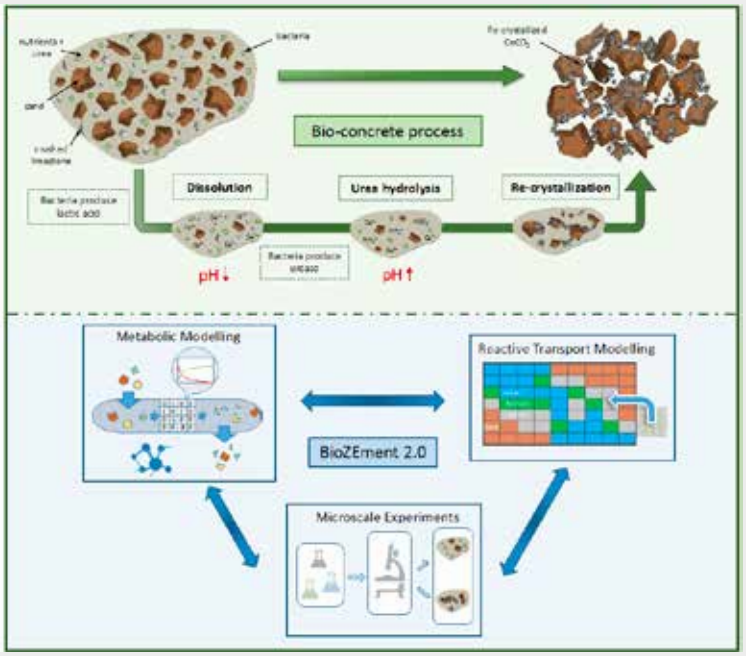
The BioZEment concept is based on the dissolution and precipitation of calcium carbonate, induced by selected, non-pathogenic bacterial strains. Our ambition is to combine systems biology metabolic modeling of bacterial strains, advanced microbiological techniques, material characterization, and geochemical reactive transport simulations, to gain in-depth understanding of the bio-geochemical system in order to optimize it with respect to production time and material properties. We will also investigate the regulatory, environmental and consumer aspects that may influence the future use of the product.

ACTIVITIES

The project started in April 2017 with a kick-off meeting in Trondheim, with all project partners present. All 3 PhD positions were filled by the end of September 2017, and all partners were gathered for the first project meeting in Oslo in November, where we made integrated plans for the next 6 months and established routines for data management, communication and outreach. Continued interdisciplinary communication is ensured through weekly online meetings.

ACHIEVEMENTS

The first months of the project have been focused on developing experimental and numerical models. Our first microbiological experiments are running and producing data, and we have made progress in the techno-economic and consumer studies. The innovation aspect of the project has been continued though our contact with Inven2 and the presentation of the project at an industry-science meet-up organized by Inven2 and SubseaValley. The project was also presented at the Goldschmidt geochemistry conference in Paris in August 2017.



dCod 1.0 — Decoding the systems toxicology of Atlantic cod activities

This year, several large scale in vivo experiments with Atlentic cod(Gadus morhua) has been performed by dCod 1.0 partners at UiB and UiO/NMBU, in addition to field sampling of cod by IMR and UiO. This has resulted in more samples available for environmental chemistry, and for omics analyses. Along with in vitro experiments with precision-cut cod liver slices at UiB, these activities have generated an initial series of large datasets for our data-hungry bioinformaticians and mathematicians. Bioinformatics activities have focused on data management issues, ensuring that dCod data and metadata from the project are handled and stored in line with the FAIR (findable, accessible, interoperable, reusable) principles, and, together with ELIXIR, improving the annotation of the cod genome.

The Research School "Fish Ecotoxicology in silico" was successfully organized by Malin Celander (UG) in Kristineberg, Sweden, August 2017. Here, the majority of dCod PhD students and postdocs participated in discussions and lectures of societal and experimental relevance, lead by several dCod scientists. During the PI's sabbatical tours in the spring and fall of 2017, the dCod project was presented at various seminars and meetings, and contacts have been established with relevant scientists, across USA and in Canada. Also, project members have participated in public outreach activities with focus on RRI, such as "Passion for Ocean" science festival in Oslo and "Fishackathon" in Bergen.

ACHIEVEMENTS

The dCod 1.0 project was presented at various conferences and seminars in Norway and abroad. Main conferences this year have been the NSFT Winter Meeting at Beitostølen in January (2 platforms, 6 posters), PRIMO 19 in Matsuyama, Japan, in July (3 platforms, 3 posters), and the ICSB conference in Virginia, USA, in August (3 presentations). Good communication between experimental biologists and bioinformaticians and mathematicians in the project is essential to reach the goal of integration and transdisciplinarity. Integration of activities and the creation of a shared language has been a focus, and is achieved through biweekly meetings in Bergen, with other partners participating by skype.

AMBITIONS

Our ambitions for 2018 is to continue the integration of experimental data with modelling and large-scale bioinformatics analyses. One aim is to generate a draft metabolic reconstruction of cod liver, in collaboration with Prof. Bernhard Pálsson's group at UCSD, and with the DigiSal project, a contact that was established in 2017. Another ambition is to increase the involvement with stakeholders and user groups as part of our RRI focus.

dCod postdoc Zhanna Tairova (UiO) explains cod biology during the Passion for Ocean science festival in Oslo, Sept. 16, 2017

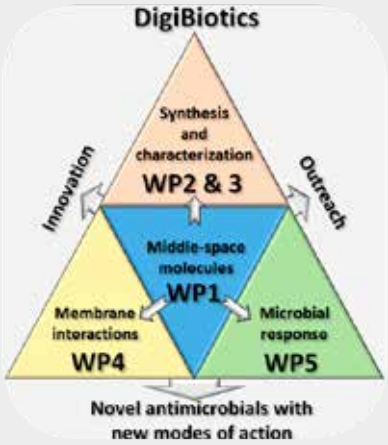
DIGIBIOTICS

Digital discovery of antimicrobial molecules from marine Arctic resources with reduced risk of triggering resistance

Antimicrobial resistance is currently causing around 700 000 deaths annually, with an estimated rise to 10 million over the next 30 years. Continuous development of antimicrobial compounds with new modes of action is essential to reduce the threat posed by antimicrobial resistance. **DigiBiotics** will meet this challenge by exploring new compounds inspired by marine Arctic natural products and developing novel experimental and computational methods for determining molecular structure and dynamics, and interplay with bacteria. This will allow for a better understanding of drug-target interactions and provide an atomic resolution for drug development against novel targets. Promising compounds will be refined to a level suitable for continued sustainable drug development in the pharmaceutical industry

The goal of DigiBiotics is to translate innovative scientific discoveries into commercially attractive propositions by combining in-depth scientific knowledge with a broad understanding of the requirements of successful drug discovery and development.

- Digitally mine genomes, isolate and identify novel antimicrobial molecules from Arctic marine microorganisms with a selection of compounds less prone to trigger resistance development
- Create, develop and validate experimental and computational methods for determination of molecular structure, absolute configuration and conformation.
- Provide, through new computational and experimental methods, an in-depth understanding of structure-activity relationships for "middle-space molecules" enabling optimization of their biological activity
- Compute quantitative structure activity relationships (QSAR) for knowledge-driven refinement of antimicrobial molecules into compounds with acceptable pharmacokinetics, optimizing potency, absorption, distribution and metabolic properties.
- Define the microbial targets and resistance development to provide feedback for refined design.



To successfully achieve the main objective in the realm of novel antimicrobial compounds, we have identified four scientific challenge areas that need to be pursued through frontier research using and extending "state-of-the-art" enabling technologies, i.e. 1. discovering novel hits from underexplored sources, 2. the rapid characterization and correct determination of the absolute configuration, 3. understanding the membrane interaction/mode of action at an atomic level, and 4. optimization of the pharmacological properties and resilience towards resistance development. Digibiotics was awarded 6 postdoctoral researchers that complement 6 PhD-positions provided by UiT, The Arctic University of Norway. Later an Industry PhD-student and 1 PhD-student and a postdoctor funded by FRINAT joined the consortium. As the official startup of DigiBiotics is January 2018, the activity in 2017 has been dedicated to preparatory work. Hiring of personnel has been the main focus and by year end 2017 all PhD-students as well as two postdoctors have been appointed. The organizational structure of the consortium has also been established. Furthermore, the consortium has had meetings with representatives of the Digital Life Norway management. DigiBiotics were also honored with hositing the Volterra lecture of 2017, a very successful lecture, "Basic Research and industrial translation-the ultimate blend", by Inger Sandlie.

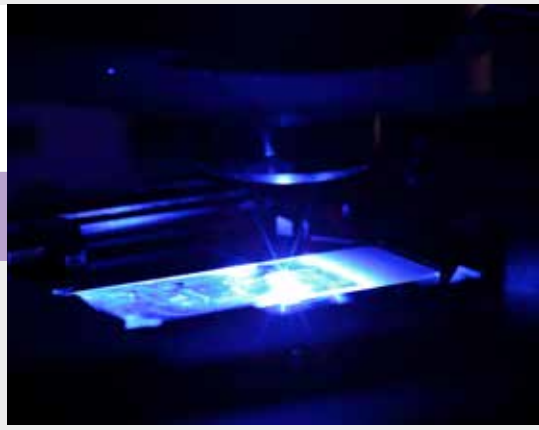
DigiBrain – from genes to brain function in health and disease

Brain related disorders and disease are among the largest health challenges in the world today and will only increase with an aging population. Our current understanding of underlying mechanisms of brain disorders is limited, and this often leads to inefficient treatment with negative side effects. Through large-scale Genome Wide Association Studies (GWAS), mapping gene variants from large groups of patients with matched controls, core members in DigiBrain together with international partners showed some few hundred gene variants occur more often in patients with schizophrenia compared to controls (Ripke et al., 2014). Many of these genes are involved in how neurons communicate with each other. In the DigiBrain project, we aim to reveal the relationships between the risk gene variants and neuron function in order to explain some of the basic underlying mechanisms of clinical findings of schizophrenia and bipolar disorders.

Using a multidisciplinary approach, we have a platform integrating mathematical modeling, experimental neuroscience and clinical measurements to reveal basic mechanisms which may in turn lead to the discovery of novel drug targets and improved treatment. Combinations of gene variants, all known to be specific to the central nervous system, are assessed in mathematical models of neurons in order to explore their effects on neuron function. This is compared to measurements from human patients and in targeted animal and cellular experiments.

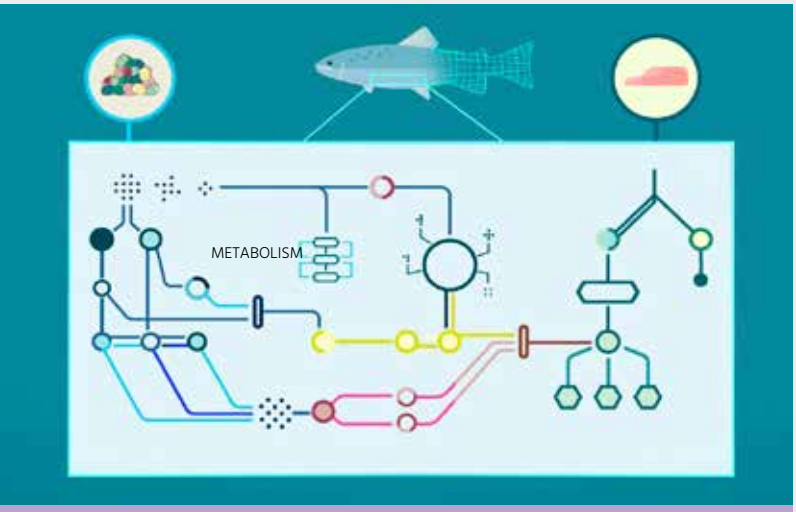
We have collected DNA samples and recorded brain activity from more than hundred patients and healthy volunteers, and we can now evaluate these results in light of the genetic risk profiles of these individuals. Almost half of the individuals have also donated skin biopsies from which we have reprogrammed and derived into neurons. This allows us to explore the impact of these donors' particular genetic make-up (their collection of variations across all genes) on the activity of the cells and then to compare this to the brain activity recordings we obtain from the patients. The effects of selected risk genes are also being explored experimentally in animal models. Finally, we are establishing gene editing tools that will enable us to directly manipulate target gene variants within cells and explore the resulting impacts of these manipulations on the cells' activity. As of the end of 2017, the first seven publications have been published from the project. Together, the various components and methods in this project will facilitate a better understanding of brain function, both in health and disease, as they explore the effects of genetic variations in target genes from the molecular, to cellular, to organism levels.

Figure 1: DigiBrain – investigating brain-related disorders on different levels, from genes to neuron models to animal models and humans



DIGISAL – TOWARDS THE DIGITAL SALMON

The Digital Salmon will be a library of life process models in the salmon body, to quickly construct suit-tailored simulations to compute effective use of resources, for food security, fish welfare and human health.



Can we compute what to feed farmed salmon?

ACTIVITIES

Outreach. We made an animated film explaining DigiSal in simple words and pictures. The project featured in two radio shows/podcasts and three national newspaper interviews, gave talks on societal aspects of digital production biology at a breakfast meeting by the Biotechnology advisory board, and on innovation opportunities to the Life Science Cluster.

Metabolic modelling. A computer model of the salmon's biochemical reaction network will be published in 2018. This requires improved annotation of the salmon genome, mapping genes to proteins and reactions in a quality-controlled way which tracks the evidence for each annotation. Our work on this with Dutch partners resulted in one publication and one preprint last year. We developed a system for automatic testing of metabolic models through a graduate internship by a Dutch student.

Experiments. Gene editing to knock out omega-3 genes in salmon shows promise for future validation of hypotheses derived from the modelling work. Rearing wild trout eggs under varying omega-3 supply produced a rich dataset for identifying relevant genetic variation that may also be present in salmon. We also collected samples from collaborating projects: one fish-tank experiment on feed efficiency, and another on liver-slice culture to evaluate lipid metabolism.

ACHIEVEMENTS

The DigiSal animated film has proven its value in making a complex topic accessible for the general public in the wider context of food security and sustainability. Furthermore, DigiSal is involved in five scientific papers ranging from information science to gut microbiota to omega-3 biology, exemplifying the broad outlook of the project.

AMBITIONS FOR 2018

Starting from a core model of liver metabolism, we will develop model scenarios for gut and muscle to interpret omics data on gene expression and abundance of biomolecules. Furthermore, we will quantify the energy costs of salmon's transition to seawater using the model's thorough account of ion and redox balance.

In 2018 we will engage society in discussion about digital production biology, through an industry workshop and a reference group with members including environmentalists, wild-salmon enthusiasts, aquaculture skeptics, and industry. Although better aquaculture is a main motivation for digitizing knowledge of the salmon body, it will also greatly increase understanding of wild salmon fishes, with applications in ecological research and management.

INBioPharm – Genes from marine microorganisms to combat antibiotic resistance

Most antibiotics in medical use today are derived from bioactive chemicals produced by microorganisms in nature.

However, rapidly spreading antibiotic resistance among pathogenic bacteria craves for new strategies for a more rapid and targeted discovery of new bioactive compounds and develop them into medicinal drugs to secure treatment of life-threatening bacterial infections also in the future. The INBioPharm project will deliver a new modular technology platform that will, with high throughput, exploit the hidden potential in natural microbial biodiversity, starting with a unique collection of marine Actinobacteria from the Trondheim fjord. Identified novel natural products will be produced in designed Streptomyces "Superhost" strains and characterized with respect to their potential for future use in medical applications.

Activities, Achievements, Ambitions. In 2017, work in INBioPharm focused on the deep analysis of the genome sequences of approx. 1.200 selected marine isolates with respect to their taxonomic and functional diversity. Using advanced bioinformatics tools developed by and together with our international collaborators, more than 24.000 biosynthetic gene clusters (BGCs) encoding potentially new bioactive compounds were identified and grouped along with biological activity and phylogenetic data in a new, searchable database. First, DNA libraries of promising BGCs from a selection of isolates were generated, technology for their transfer to suitable production strains established, and first model BGCs successfully expressed in our main production host, Streptomyces coelicolor. A high-quality metabolic network model of this bacterium was built and computer predictions tested against experimental data. Simulations have identified a set of gene modification to further improve the strain's capabilities and flexibility to produce new chemistry based on introduced BGCs. To identify structurally novel bioactive compounds among the many thousands of candidates, a novel molecular networking platform, integrating mass spectrometry data and BGC sequence-based compound prediction, was developed and tested. In the next project period, this platform will be further improved and extended into an efficient, generic, multi-layer platform for multi-omics data integration, along with lifting BGC cloning, transfer into S. coelicolor, and expression to the high throughput level. Antibiotic precursor supply for novel BGC-based bioactive compound production in S. coelicolor will be optimized based on a continuous gain in systems-scale knowledge derived from deep phenotyping and sophisticated computer simulations that incorporate and integrate multiple levels of experimental data.

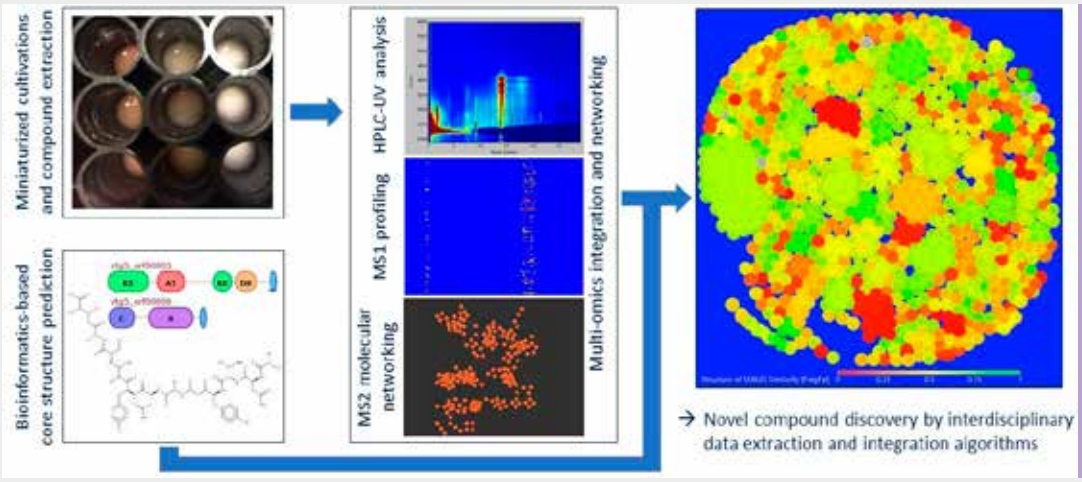


Figure: Identification of novel BGC-encoded natural products in INBioPharm by multi-omics integration and molecular networking. Structure of SMILES Similarity color coding in the right panel depicts large to small differences of one selected chemical structure in relation to all other structures in a selected database of known and unknown compounds with a color scale ranging from red to green.

LAB-ON-A-CHIP (LOC) — BIOPHOTONIC SENSOR PLATFORM

The goal of the project is to develop a LOC label-free biophotonic sensor platform to perform highly sensitive and selective multiplexed diagnostic tests with microliter volumes. Laboratory functions are realized on a chip the size of a stamp. Microfluidic channels guide the transport of fluids containing biomarkers to the multiplexed sensor elements. Surface functionalization of each sensor element with specific capture moieties mediates detection of the targeted biomarker. Our final LOC sensor demonstrator will have four multiplexed sensors that are surface functionalized for three different target biomarkers. If the LOC platform is successful, a large number of biomarkers can be measured enabling numerous biomedical applications.

ACTIVITIES

Ring resonator, photonic crystal and grating sensor configurations have been simulated and fabricated on a silicon-on-insulator platform (SOI) using photolithography techniques. The surface chemistry on the photonic sensor is being optimized to develop the best 'chemical recipe' for binding antibodies to the sensor surface to achieve high sensitivity. To do this, we measure surface hydrophobicity, surface roughness and chemical content. We are also developing methods to evaluate interactions between immobilized antibodies and their antigens using force spectroscopy and evaluating resident times with fluorescently labeled spheres functionalized with antigens. By combining these measurements with sensitivity tests on the photonic sensor, we aim to identify the parameters that are important to optimize. A methodology for prototyping PDMS microfluidic channel networks for controlling sample flow over the biosensor has been established.

ACHIEVEMENTS

Single channel sensors with microfluidics have been fabricated and tested with hydrochloric acid and c-reactive protein, an inflammation biomarker. The sensors have shown a shift in resonance frequency as a function of sample concentration in agreement with simulations. A flexible holder for chip assembly allowing access for fluidic inlet- and outlet tubing as well as optical access for excitation and readout of the biophotonic sensor has been manufactured in plexiglass. It permits assembly-disassembly of the microfluidic-biophotonic chip sandwich offering flexibility for functionalization, sample feed, cleaning and characterization.

AMBITION

The LOC project will pursue to create awareness through communication activities of the project and its goal amongst the target stakeholder groups. To increase sensor sensitivity and selectivity, work will continue on the photonic sensor design, functionalization protocols, and design of the microfluidics to increase biomarker transport to the sensing area. Multiple channel sensors will be designed, fabricated and tested on protein samples.

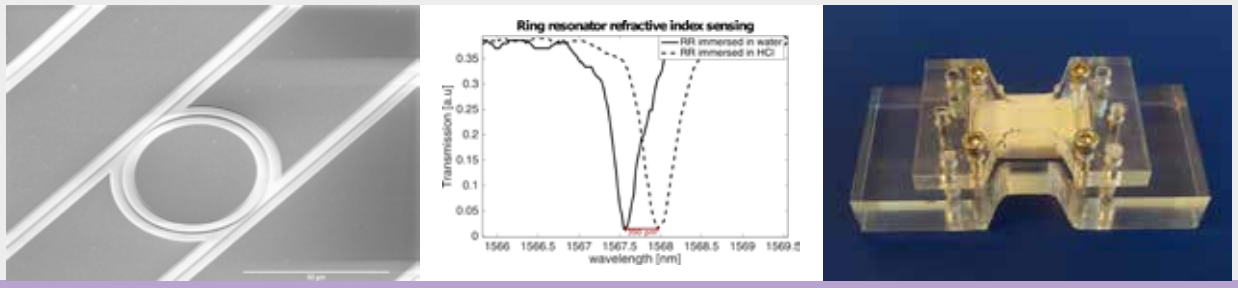


Figure: a) Single channel photonic sensor b) concentration measurement c) microfluidic chip holder

OxyMod

OXYMOD will combine life sciences (enzyme biochemistry, enzyme production technology, microbial biotechnology, high throughput screening, advanced analytics), ICT (bioinformatics, big data handling), mathematical sciences (enzyme modelling, enzyme systems modelling, process modelling) and engineering (enzyme evolution, synthetic biology) for producing efficient biocatalytic systems. We focus on developing well-functioning multiple enzyme cocktails for processing complex plant biomass, such as trees or agricultural waste, also known as lignocellulosic biomass. OXYMOD has a particular focus on studying how redox enzyme systems involved in degradation of polysaccharides such as cellulose and redox enzyme systems involved in lignin conversion interact. Analogous enzyme systems for processing of complex chitin-rich biomass may also be studied.

Using a collection of 1000 sequenced Actinomcete genomes we use bioinformatic and advanced functional screening to discover relevant redox enzymes. From characterizing individual enzymes, we will move towards studying the interactions between these enzymes and towards development of efficient enzyme systems.

The project has just started and in 2017 resources have been spent on planning, setting up management structures and, importantly, on advanced bioinformatic screening of our unique biodiversity. Based on this 2017 work, which has given us a wealth of ideas, the first series of enzyme cloning, production and characterization studies will be initiated in January 2018. Furthermore, we have initiated work on better expression systems for the enzymes, and we are setting up novel expression systems.

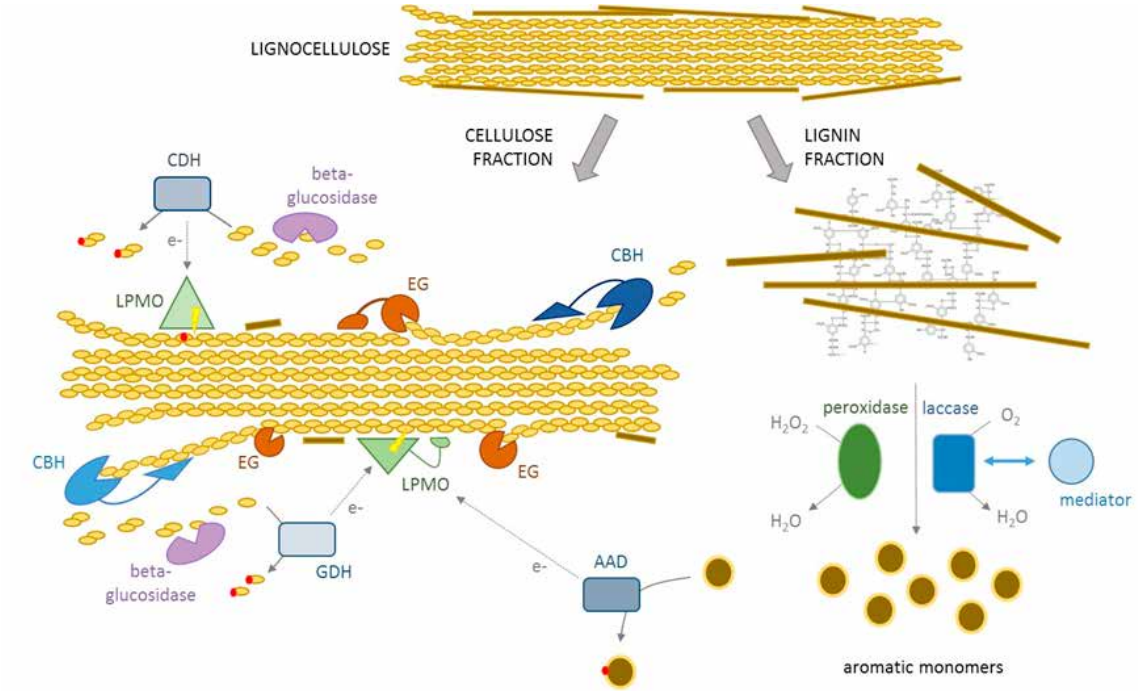


Figure: An example of an enzyme system acting on biomass. The figure shows a schematic overview of some of the enzymes known to be involved in degradation of lignocellulosic biomass. Different enzyme types appear in different shapes and colours and their abbreviated names are given (for example, LPMO stands for Lytic Polysaccharide Monooxygenase). All enzymes using or producing electrons (e-) or using hydrogen peroxide (H2O2) or oxygen (O2) are redox enzymes that likely interact with each other.

Double Intraperitoneal Artificial Pancreas

ACTIVITIES

During 2017 activities of the Double Intraperitoneal Artificial Pancreas (DIAP) have focused on developing new methods of intraperitoneal (IP) glucose sensing as well as modifying the non-invasive glucose sensor developed by Prediktor Medical AS for IP use. Animal experiments on IP absorption of insulin and glucagon are done as well as several experiments of IP glucose sensing in order to identify possible regional IP differences in absorption and glucose sensing. New technologies for glucose sensing are also explored as well as safety issues for an artificial pancreas (AP).

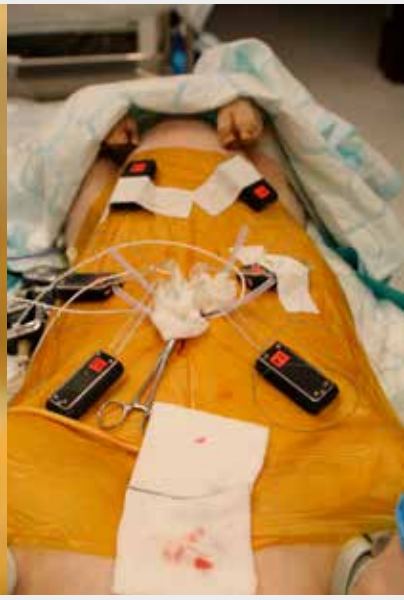
ACHIEVEMENTS

APT has been able to establish a new method to identify meals at an earlier stage by using the "Moving Horizon Estimation" approach of evaluating the glucose levels. Identifying meals as early as possible after ingestion is one of the great challenges in any AP and our novel method can be used for any AP and may be particularly valuable for the double subcutaneous approach used in most APs.

Further, the APT group has shown in an animal experiment that absorption of glucagon is faster after IP delivery compared to subcutaneous (SC) injections. This may be utilized in a double IP AP and will be explored by the APT (Artificial Pancreas Trondheim) group during 2018.

AMBITIONS

The ambition of the Double Intraperitoneal Artificial Pancreas (DIAP) project by the APT group is to make a "perfect" artificial pancreas to be used by patients with diabetes mellitus type 1 (DM1). Patients with DM1 have lost their ability to produce insulin and, hence, they are totally dependent on external supplies of insulin. APT intends to establish an external delivery of insulin that will keep the glucose levels in patients with DM1 in the normal range, i.e. the same range as in subjects without diabetes. This will be achieved by the double IP approach, i.e. both glucose measurements and insulin delivery will take place in the IP space.



Res Publica – Responsibility, practice, and the public good across Digital Life

Science policy vests high expectations in enabling technologies, such as biotechnology. The hope is that biotechnology's innovative potential can transform oil-based economies to a bioeconomy. At the same time, there is a widely acknowledged democratic deficit in the governance of enabling technologies, and developments in biotechnology are assumed to permeate many aspects of social life. This generates new questions about science, social order and the public good that the Res Publica project will analyse with a point of departure in the kind of computational biotechnology pursued in DLN.

AIMS AND AMBITIONS

Recently, the science policy idea of "Responsible Research and Innovation (RRI)" has gained ground as a response to tackle this problem of democratic deficit. Based on previous research and on experiences from working with DLN, we know that implementing RRI into practice is more demanding than anticipated in mainstream RRI scholarship and policies. Our aim in Res Publica is to identify first the kind of situations where RRI resonates with ongoing research practices. This may make RRI easier to implement. To achieve this, we will introduce action research methods to engage scientists in DLN and related actors in a learning process. Our ambition is that scientists develop a sense of ownership to the RRI concept.

Second, we intend to widen the scope of potential RRI interventions to multiple sites beyond individual research projects. This is an innovative move because we assume that RRI can only be implemented if we at the same time address the conditions in which science is made. By mapping out the socio-economic-political context pertinent to DLN, we hope to generate knowledge and explain some of the underlying factors that need to be in place for a democratic governance of science and technology. Our ambition is that science policy makers re-evaluate certain science governance tools.

ACHIEVEMENTS

Res Publica is a cooperation of the three Science and Technology Studies (STS) centres in Norway (Centre for Technology and Society, NTNU Trondheim, Centre for the Study of the Sciences and Humanities, University in Bergen, and the Centre for Technology, Innovation, and Culture, University in Oslo). In DLN context, the project is relatively little. With a budget of 10 million NOK, the resources of the three-year project cover one full-time researcher, one post doc (2 years), and one PhD. They will start to work on the project in spring 2018. The project began in October 2017 with a preparatory meeting to establish a common ground across the three project partners. November and December was devoted to recruiting the PhD, and preparing the kick off meeting in February 2018.

DLN BOARD

The Centre for Digital Live Norway is governed by a small and efficient Board. The DLN Board ensures alignment of DLN and institutional Strategies and development. It secures a birdseye perspective of the DLN Centre - pulling different work groups together. the DLN Board consists of one representative for each hub-partner, two representatives for the node partners, and two industry representatives.


Finn-Eirik Johansen - UiO
Chairman of the board


Tor Grande - NTNU


Eyvind Rødahl - UiB


Eli Aamot - SINTEF


Ragnhild Solheim - NMBU


Silvija Seres
Industry representative


Gerd Nilsen
Industry representative

DLN SCIENTIFIC ADVISORY BOARD

The Scientific Advisory Boad (SAB) cinsists of internationally renowned experts in fields of high relevance to the DLN mission, and who have a proven track record in managing large and complex academic structures. The SAB will support DLN by providing independent, credible and imaterial recommendations on academic matters, and matters concerning the internal operation of DLN as well as DLN's national network function responsibility. At the annual centre conference; DigitalLife 2017, the SAB were invited speakers.


Ulrike Felt
Universität Wien


Peter Hunter
The University of Aukland


Anne-Claude Gavin
EMBL

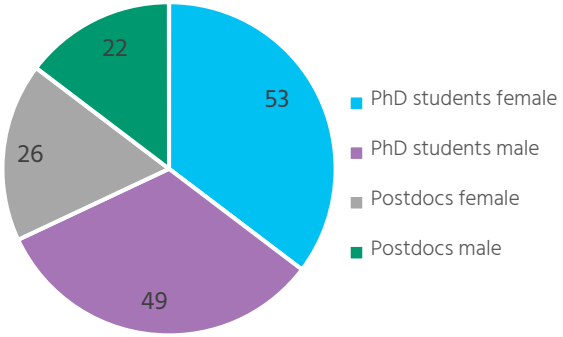

Rudi Balling
Université du Luxembourg


Vera van Noort
University of Leuven

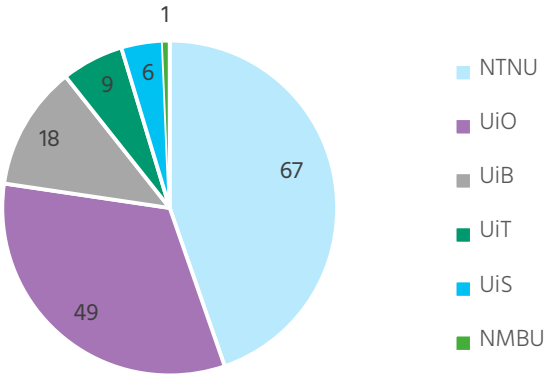

Dominique Chu
University of Kent

THE DIGITAL LIFE YEAR AT A GLANCE

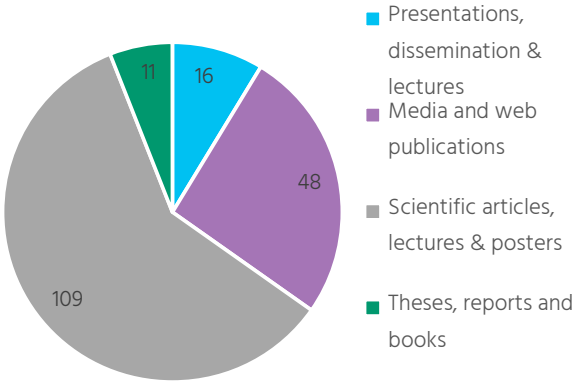
MEMBERS DIGITAL LIFE NORWAY RESEARCH SCHOOL



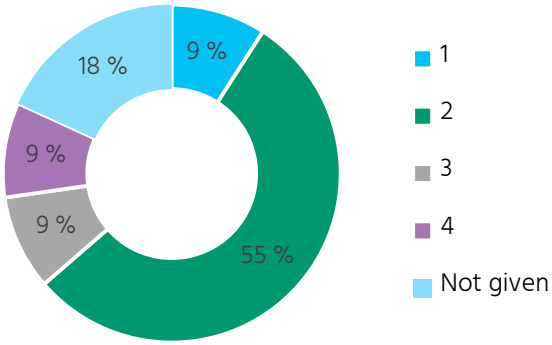
DLN RESEARCH SCHOOL MEMBERSHIP BY UNIVERSITY



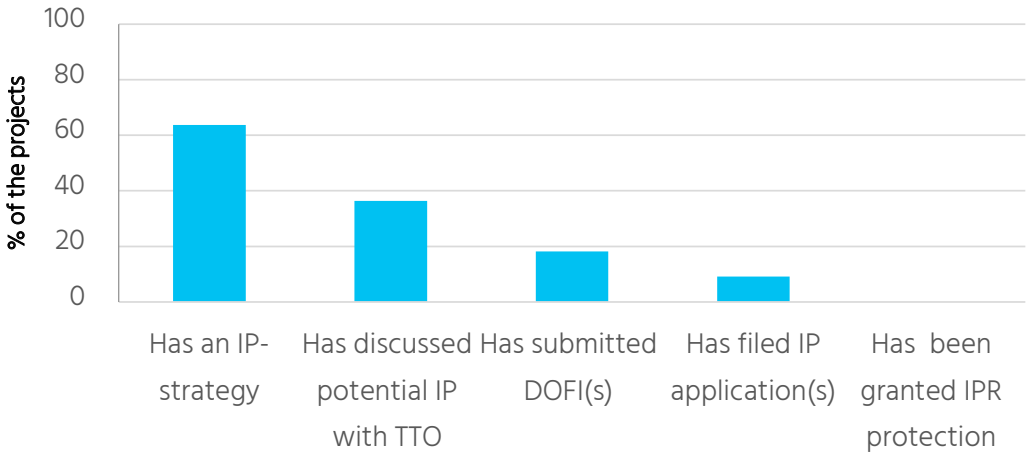
DLN OUTREACH

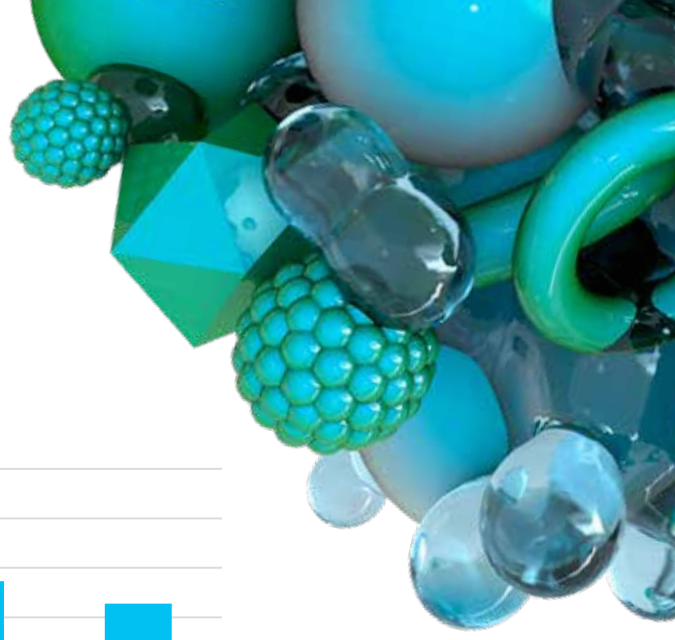


NO OF POTENTIAL INNOVATIONS/ BUSINESS IDEAS IDENTIFED SO FAR PER PROJECT

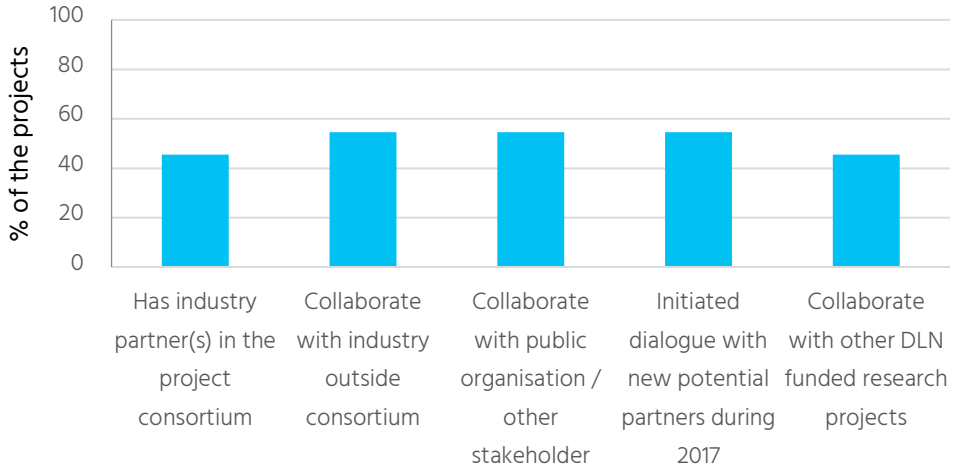


IP AND COMMERSIALIZATION

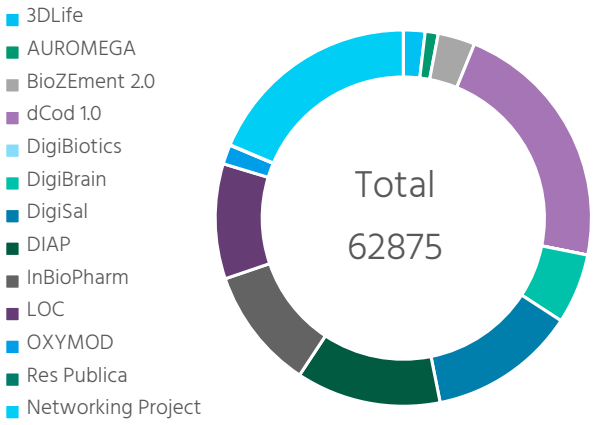




RESEARCH COLLABORATION

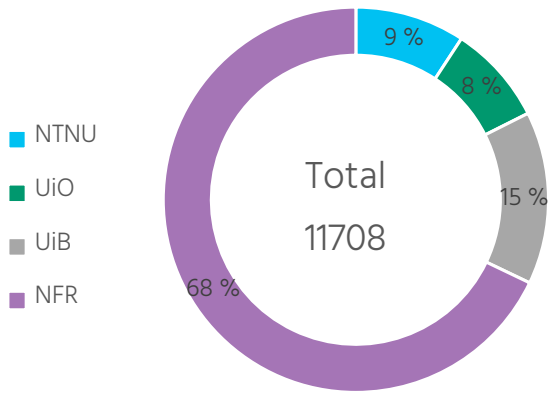


ACCOUNTS FOR THE CENTRE PROJECTS



Acounts for the twelve research projects and the centre leadership (networking project)
DIAP: Double Intraperitoneal Artificial Pancreas, LOC: Lab-on-a-chip (In x1000 NOK)

FUNDING OF THE DLN NETWORKING PROJECT (CENTRE LEADERSHIP)



DLN is funded by the Research Council of Norway, in addition to *in kind* funding from the three hub universities - NTNU, UiO and UiB. (In x1000 NOK)

INTERNATIONAL RESEARCH COLLABORATION

DLN research projects have excellent international research partners in the following places around the world.

- Auburn University, USA
- CorTechs Lab, USA
- CSIC, Spain
- EMBL, Germany
- EPFL, Switzerland
- ETH Zürich, Switzerland
- Forschungszentrum Jülich, Germany
- Institut Català de Nanociència i Nanotecnologia, Spain
- Jacobs University, Germany
- LNEG, Portugal
- NEST, Germany
- RIKEN, Japan
- RISE, Sweeden
- Stanford University, USA
- Technical University of Denmark
- UC San Diego, USA
- Universidade NOVA de Lisboa, Portugal
- University of Amsterdam, Netherland
- University of Aveiro, Poertugal
- University of Bielefeld, Germany
- University of California, USA
- University of Edinburgh, UK
- University of Maastricht, Netherland
- University of Vienna, Austria
- Varigen Biosciences, USA
- Wageningen University, Netherland
- Woods Hole Oceanographic Institution, USA

CENTRE FOR DIGITAL LIFE NORWAY WILL THANK THE FOLLOWING FOR THEIR CONTRIBUTION IN 2017

THE BIO ECONOMY REFERENCE GROUP

- Anne Cathrin Østebø, Validé AS
- Eirik Lundblad, Arctic biodiscovery
- Håvard Sletta, SINTEF
- Ingrid Lea Karlskås, NCE aquaculture
- Ketil Widerberg, Oslo Cancer Cluster
- Marius Øgaard, Oslotech/The lifescience cluster
- Odd Arild Lehne, Pubgene AS
- Olav Arne Bævre, Nibio
- Ole Kristian Hjelstuen, Inven2 AS
- Randi Taxt, BTO AS

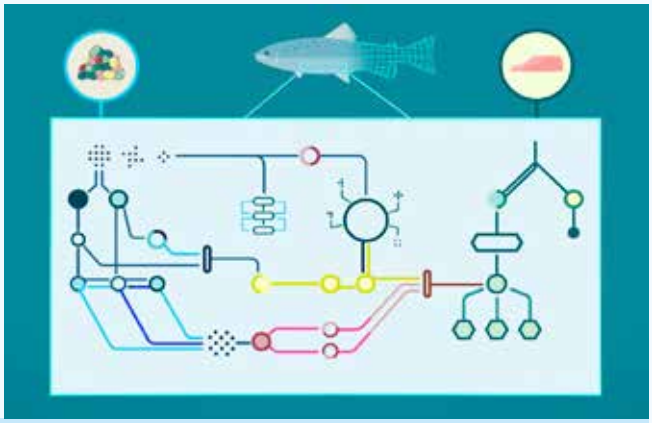
THE DLN RESEARCH SCHOOL BOARD

- Lex Nederbragt, UiO
- Gaute Einevoll, NMBU
- Inge Jonassen, UiB
- Arvid Lundervold, UiB
- Per Bruheim, NTNU
- Heidrun Åm, NTNU
- Arne Smalås, UiT
- Tormod Drenstig, UiS

THE COMPETENCE AND INFRASTRUCTURE LEADER GROUP

- Ines Heiland, UiT
- Eivind Hovig, Norwegian Radium Hospital
- Mette Langaas, NTNU
- Lex Nederbragt, UiO

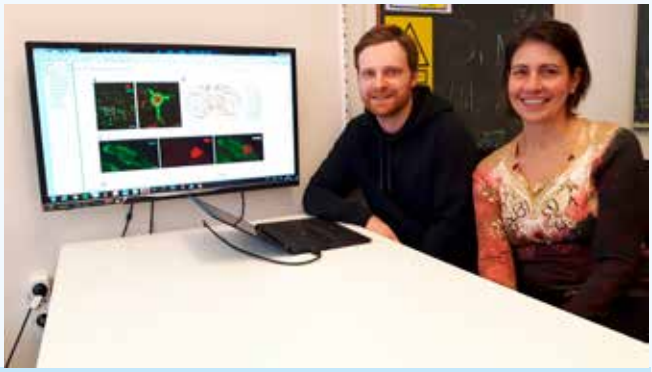
DLN AWARDS



Snapshot of the award-winning animation produced by DigiSal in collaboration with NMBU and Tor Martin Austad(Visual labs)

DIGISAL AWARDED BEST BLOG POST IN 2017

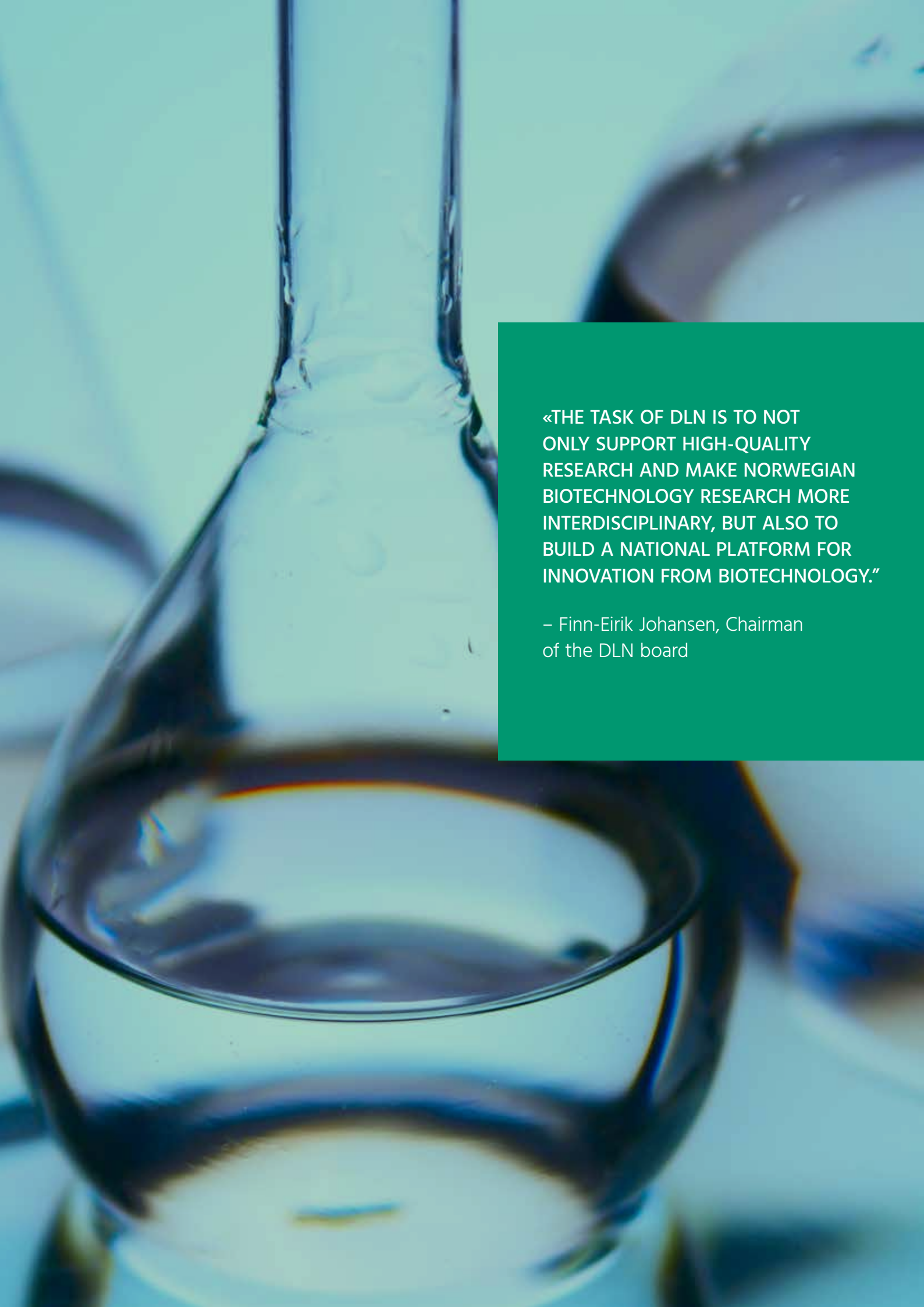
All blogposts from research projects posted on the DLN website in 2017 where considered for the best blog post. Two of them excelled in particular; Can computer simulations substitute animal research? by Marta Julia Sætra from DigiBrain, and The Digital Salmon hits the big screen from the DigiSal project. Both candidates highlight the new possibilities when using computational biology, and present it in an excellent manner. Based on the originality combined with great story-telling and visualization of a complex project, the price for 2017 is awarded to Jon Olav Vik and the production team.



Happy first author Kristian Kinden Lensjø and last author Marianne Fyhn, project leader of DigiBrain.

DIGIBRAIN AWARDED BEST TRANSDISCIPLINARY PAPER IN 2017

This year's best transdisciplinary paper is awarded to Lensjø et al, J. Neuroscience. The paper shows how extra cellular matrix (ECM) affects inhibitory activity and thereby regulates plasticity. The implications from the experimental data were tested in network simulations, which gave support to the paper's conclusion.



«THE TASK OF DLN IS TO NOT ONLY SUPPORT HIGH-QUALITY RESEARCH AND MAKE NORWEGIAN BIOTECHNOLOGY RESEARCH MORE INTERDISCIPLINARY, BUT ALSO TO BUILD A NATIONAL PLATFORM FOR INNOVATION FROM BIOTECHNOLOGY."

– Finn-Eirik Johansen, Chairman of the DLN board

CREDITS

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NORWAY

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