CENTRE FOR
DIGITAL LIFE
NORWAY

ANNUAL REPORT
2019

CENTRE FOR DIGITAL LIFE NORWAY

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From the Centre leader

Dear reader,

It is my privilege to present the 2019 annual report of the Centre for Digital Life Norway (DLN). It is middle of March 2020 as I write this introduction and for the past few days the world has completely changed due to the pandemic outbreak of the SARS-CoV-2 coronavirus. We have an extreme situation with most societal functions closing down and currently it is not possible to predict how this situation will develop for the next weeks and even not for the rest of 2020. We suddenly witness how extraordinarily complex and fragile the global interdependences are on which our quality of life depends.

DLN is a research policy experiment whose aim is to produce tested experience in how interdisciplinary collaboration between the molecular life sciences and other disciplines can enhance the production of knowledge that is needed to effectively engage with grand societal challenges. As the corona pandemic in a brutal manner shows, the well-orchestrated interplay of many scientific disciplines is vital. This demands new ways of working across academic disciplines and it takes a fair share of experimentation to learn how to harness synergies in this more complex landscape of research governance. Societal challenges are usually not as immediate and extensive as the corona pandemic, yet many of the challenges DLN researchers seek to address are urgent because of the sheer magnitude of their consequences. Take for instance antimicrobial resistance or the need to thoroughly green our economies, two of the topics researched in the Centre; they are crises in slow motion that not only require more research, but also new approaches to the organization of science.

During 2019 DLN has grown to a respectable 36 research projects and some 350 junior researchers partaking in activities of our research school. It is not size alone that matters, but the fact that the Centre has developed into a truly national community. This is geographically evident, as our projects are from Stavanger in the South to Tromsø in the North, and from Ås in the East to Bergen in the West. With this many researchers and projects, we have seen a strong increase in the number of collaborative initiatives between projects, including joint seminars and meetings, sharing of competences, and other research activities. The Centre's cross-project collaboration support helped cancer researchers apply topological data analysis methods that were developed in a project studying fish biomarkers; to harness a lab-on-a-chip biophotonic platform for investigating fish plasma biomarkers; and to test leukemia drug sensitivity in 3D-culture assays. These and many other projects are all in line with DLN's vision to promote transdisciplinary research through collaboration.

It is not a regular occurrence that different universities collaborate nationally to this extent. And this makes DLN an ideal platform for testing out new ways of organizing and supporting science. Take for instance innovation support. In close collaboration with the Research Council of Norway (RCN) we launched a new initiative in 2019, "a roadmap for academic research-intensive innovation". The project aims to use DLN as a blueprint for promoting more innovation in digital biotechnology. We are sure that this will benefit all current and future DLN research projects and researchers. It will offer support to ensure good practices when seeking innovation potential in parallel with conducting excellent science.

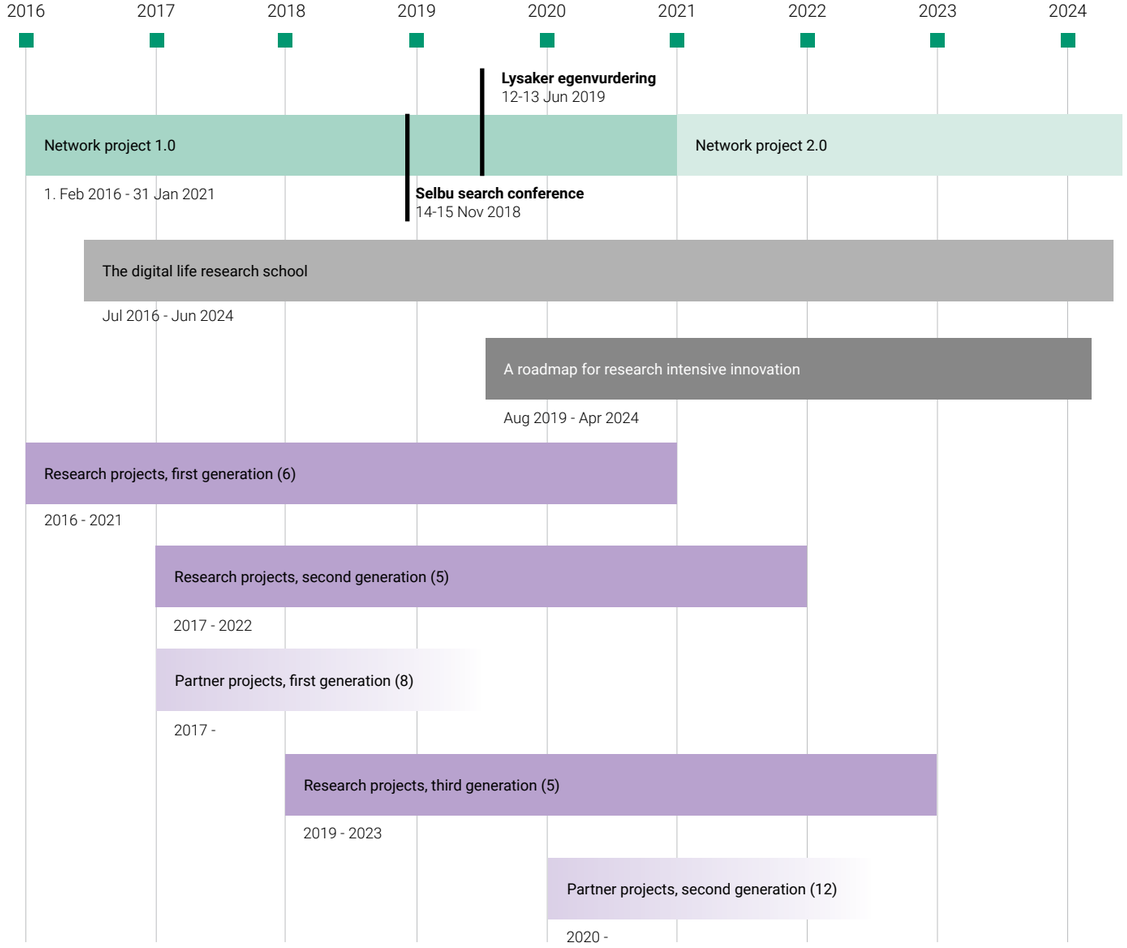
Trying to summarize this annual report would do no justice to the diversity of research our projects are doing, nor to the many processes underway to strengthen transdisciplinary collaborations around digitization and modelling in biotechnology, let alone the extensive activities to shape the next generation of researchers. You can explore all of this in the following pages.

For us in the Centre it is encouraging to see that there is a strong wish among Centre member projects, the RCN, the leadership of our host institutions, and other stakeholders for us to continue our efforts to build DLN into a strong and valuable national Biotechnology Centre. Following a self-assessment conducted together with the RCN in June 2019, the Enabling Technologies Board approved the funding of a continued DLN2.0 after the current funding period ends in 2021.

In parallel with the big concerns and uncertainties we share with everyone now with respect to the global corona pandemic situation, we would also express that we are highly motivated to enhance The Centre for Digital Life Norway further in 2020. We are already enthusiastic to continue this important national collaboration beyond 2021 and into the future.

Trygve Brautaset,
Centre leader

The Digital Life timeline



Comments from the chairman of the board

The vision of Digital Life Norway (DLN) is "Convergence for Innovation" and our core mission is to transform the Norwegian biotechnology landscape in several ways. Like other "moon shots", this is obviously an ambitious and complicated task. DLN consists of a Network Project, Research Projects directly funded by the Research Council of Norway, and Partner Projects which have other funding sources. What sets the projects apart from other large and complex research projects is the support they have from the DLN network. Ultimately, the success of DLN will be evaluated on the basis of the success of the research and partner projects.

DLN was founded in 2016 and since then the network project has been working toward its specific mission of enhancing the value of the research and partner projects. Two main themes have stood out since the beginning: Transdisciplinarity and Responsible Research and Innovation (RRI). DLN helps the individual research groups navigate these challenging issues by facilitating workshops, training sessions, seminars, meetings, and advising. Another issue that is difficult for individual research groups to handle is the data tsunami. This wave was certainly on its way when DLN was initiated, but, it is fair to say, has hit in full force by now. Helping researchers cope with data overload has become a major endeavor for DLN.

DLN is run by its owners, seven university and research institutions, in collaboration with the Research Council of Norway. Early on it became clear to these owners that more effort needed to be devoted to the vision's objective of innovation in order to enhance the value of DLN research and partner projects. In 2019, they initiated phase 1 of an auxiliary innovation project. Phase 2, scheduled to start in 2020, will integrate with the network project.

For enhanced innovation to take place, convergence is not only needed among disciplines, but also among institutions and sectors. To the board, an important value of DLN is its function as a bridge between these groups. This has been particularly effective among research institutions up until this point, but we anticipate a greater involvement with other sectors in the future. We are pleased that DLN has become a well-known entity and important voice in Norwegian biotechnology research, a first step toward transforming the landscape.

Finn-Eirik Johansen, Chairman of the board

Two more Digital Life researchers awarded PhD

Two PhD candidates in Center for Digital Life Norway partner projects who were awarded their doctorates in 2019. Xiaoran Lai and Odd Martin Staal both worked on transdisciplinary healthcare related research supported by DLN's collaborations. DLN is proud to have contributed to their research and wishes them the best in the next step of their careers.

XIAORAN LAI: PERSONALIZED BREAST CANCER THERAPY

Xiaoran Lai worked in the Center for Digital Life Norway partner project Big Insight. He defended his PhD thesis titled "Modelling, inference and simulation of personalized breast cancer therapy" on October 25th at the University of Oslo.

Lai's research demonstrates the effectiveness of using computer simulations to optimise personal treatment and lays the foundation for a potential future program to deliver a robust clinical diagnostic tool.

Mathematical modelling and simulation tools are an attractive time- and cost- effective approach to determine optimal therapy for individual cancer patients. Current models can address pharmacokinetics and pharmacodynamics of anticancer medicine at various spatial and temporal scales and simulations can explore many treatment regimens to identify optimal plans with minimal toxicity. However, individualising a model to each patient requires separate estimation and validation of each parameter, and the runtime of simulations remains too slow for practical clinical applications.

In his research, Lai used data from a recently published neoadjuvant clinical phase II trial in patients with advanced breast tumours where histological, magnetic resonance imaging (MRI), and molecular data were collected before, during, and after neoadjuvant treatment. From this data set he was able to demonstrate that a mathematical model designed for a specific type of cancer, integrated with routinely-collected clinical data, is feasible. His model was robust enough to simulate and predict various responses using individual data, and the collected data were sufficient for the purpose of validation and personalisation of the model.

ODD MARTIN STAAL: UNDERSTANDING BLOOD-GLUCOSE DYNAMICS

Odd Martin Staal worked in the Center for Digital Life Norway project Double Intraperitoneal Artificial Pancreas. He defended his PhD thesis, titled "Blood glucose dynamics: Identification, smoothing and real time estimation in free-living settings", on May 10th at the Norwegian University of Technology and Science. Staal's project focused on creating individualized, real-time BG dynamics models based on data from free-living settings to help people with diabetes properly control their blood glucose (BG) levels.

Diabetes currently affects about 9% of the world's population, and causes loss or impairment of the body's ability to control blood glucose. People with diabetes require frequent BG measurements and medications, including insulin injections, to keep their BG as close as possible to the normal range. Dynamic models that describe BG have improved our understanding of the physiology of diabetes and helped us develop external systems to control BG. However, glucose dynamics is highly person-dependent, so it is desirable to individualise the BG dynamics model to the patient data.

One potential way to individualise the models is to use the large amounts of free-living data collected by the Continuous Glucose Monitors and insulin pumps that many people with diabetes use. However, the only internal body measurement available in these data is the glucose concentration, whereas many models require more measurements (e.g. of plasma insulin) to avoid observability and identifiability problems. Another challenge is that the quality of the data from free-living settings is frequently poor, with missing data and other errors occurring both in the glucose data and in the logged meal data.

Staal addressed these challenges and published his results related to glucose data cleaning, glucose sensor characterisation, identifiability analysis in blood glucose dynamics models, and meal detection in glucose data. This work contributes to Prediktor Medical's development of products for blood glucose measurement and prediction.

The research projects

Digital Life Norway is proud to include 36 member projects from research organizations throughout Norway. They are interdisciplinary research consortia that draw on expertise in fields as diverse as the molecular life sciences, computer science, physics, engineering, as well as the social sciences and humanities to develop or better tailor pharmaceuticals, investigate more sustainable resources for the food system and industry, and critically examine the governance of biotechnology research in Norway. In the next few pages, the researchers share the details of their work and highlight achievements from the past year.

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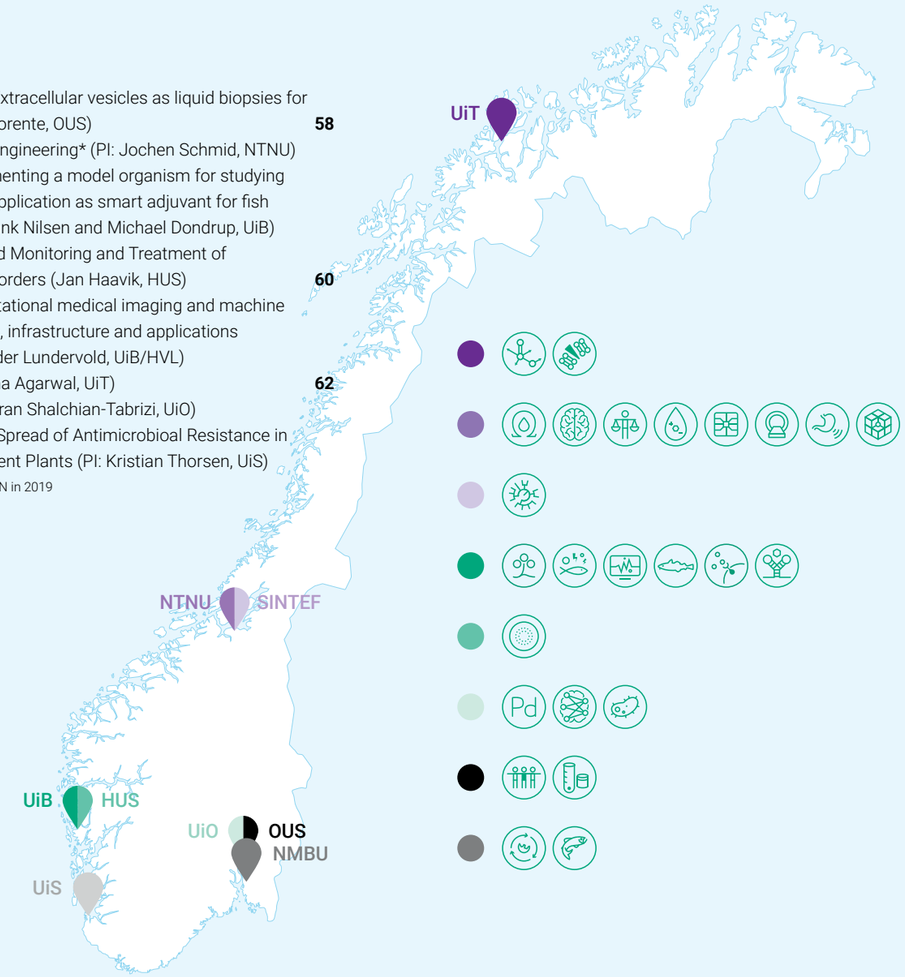
* projects having joined DLN in 2019



The vibrating blade microtome (Leica VT1200) used to produce precision-cut slices from unfixed liver tissue of Atlantic cod and other fish species.

Photo: Marta Eide.

dCod 1.0

- Decoding the systems toxicology of Atlantic cod

PROJECT LEADER: ANDERS GOKSØYR **INSTITUTION:** UNIVERSITY OF BERGEN

The purpose of the dCod 1.0 project is to gain a deeper understanding of how Atlantic cod handles environmental stress, especially from chemical pollutants, by investigating the cod's response to stress at the transcriptomic, proteomic, and metabolomic level. During 2019, our research focused on developing a draft metabolic reconstruction of the cod, using the part of the genome called the "chemical defensome" as the starting point. In addition, we are developing a mathematical model of lipid metabolism in the cod liver. Another track is a comparative analysis of the chemical defensome of Atlantic cod against four other model fish species used in toxicological research: zebrafish, medaka, fathead minnow, and three-spined stickleback. To support in these activities, we have developed a set of computational tools that can help us and others to analyze and find patterns and features in large datasets.

The metabolic reconstruction was inspired by a DLN cross-project funded workshop at Finse 8-9 April together with the DigiSal and AurOmega projects, and with invited speakers from Chalmers University in Sweden. In 2019, DLN also began cross-project funding for investigations into the application of Lab-on-a-Chip technology to dCod 1.0 reagents, and promising results have come out of this.

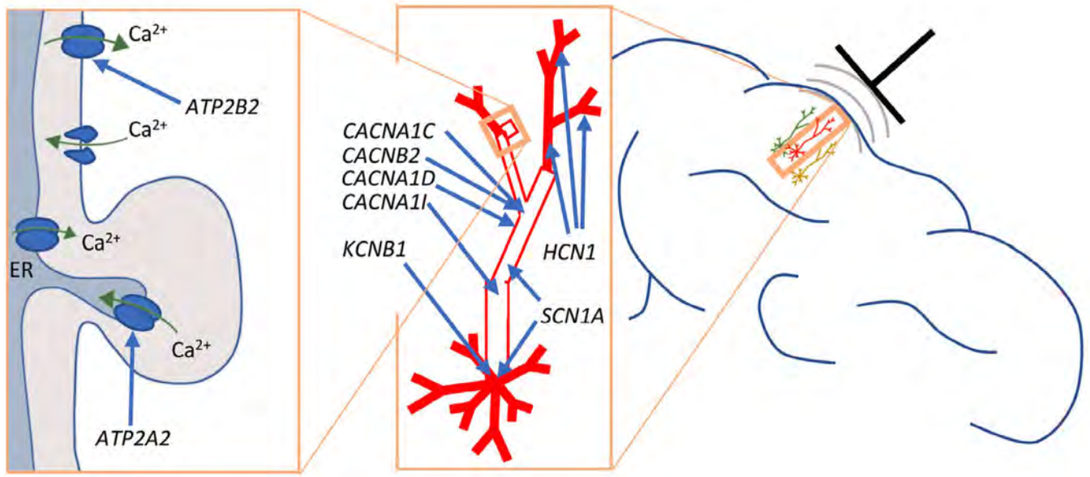
In addition to the Finse workshop on metabolic reconstruction, we held our 3rd Winter Workshop at Beitostølen in January. The workshop was organized as a satellite meeting to the Norwegian Society of Pharmacology and Toxicology's Winter Meeting, where we also had a special dCod 1.0 session. PhD student Karina Dale (UiB) won the Best Presentation Award in Toxicology at the meeting. Our 4th Winter Workshop was held 11. December in Bergen, where dissemination plans for the final year of the project were in focus.

One highlight of 2019 has been the large participation of dCod 1.0 associated students and partners at the 20th International Symposium on Pollutant Responses in Marine Organisms (PRIMO 20) in Charleston, South Carolina, USA, 19-22 May, with more than 200 participants. Members of the dCod 1.0 project presented 11 platform presentations and four poster presentations during the conference. As a bonus, dCod 1.0 PhD student Siri Øfsthus Goksøyr (UiB) was awarded the Founder's Award for best student presentation during the conference, for her talk "Assessment of endocrine disrupting effects of bisphenols in Atlantic cod (Gadus morhua) using luciferase reporter assays and precision-cut liver slices".

Another highlight was the Fish Under Stress @Runde summer school. For five days during midsummer (24-28 June 2019), 15 PhD students and postdocs gathered at Runde Environment Centre outside Ålesund to learn about systems biology, mathematical modelling, and RRI aspects of their own research. The students came from UiB, UiO, NMBU, UiS, NTNU, Nord University, Nofima/DTU, Woods Hole Oceanographic Institution (USA), and Istituto Oswaldo Cruz (Brazil), representing both Digital Life Norway Research School and Nansen Legacy Research School. Thirteen scientists covering different aspects of marine stress and mathematical modelling joined the course as lecturers, tutors, and discussion partners for the participants. This was the second summer school organized by the dCod 1.0 project and was reported to be highly successful.

By transdisciplinarity we understand the emergence of higher-level understanding and creativity when people from several disciplines meet and work together. For us this is important, because the field of environmental toxicology is inherently multidisciplinary, and because our results are important for meeting societal challenges such as the UN Sustainable Development Goals (SDGs).

Our project creates value for society by developing deeper understanding of pollution's effect on ocean health, and by developing new tools for environmental management.



"In the Digibrain project, we have built a subcellular model of the intracellular signalling cascades for post-synaptic plasticity in the cortex (Mäki-Marttunen et al., submitted). This model will be used to study the effects of genetic variants in schizophrenia-associated genes on the induction of plasticity. Thus, we will be able to map genetic data to those disease phenotypes that are related to deficits in cortical plasticity." – Tuomo Mäki-Marttunen

DigiBrain

- from genes to brain function in health and disease

PROJECT LEADER: MARIANNE FYHN **INSTITUTION:** UNIVERSITY OF OSLO

Brain related disorders and disease are among the largest health challenges in the world today and the challenge will only increase as the population ages. However, current understanding of underlying disease mechanisms is limited, hampering the urgent need for development of novel treatments. In the DigiBrain project, researchers are taking a novel interdisciplinary approach in an attempt to identify links between neural function and the gene variants identified in schizophrenia and bipolar disorders. The main aim is to establish a platform enabling transdisciplinary research including genetics, EEG measurements, stem cell and animal experiments, and mathematical modelling. The long-term hope is that such knowledge will contribute to the development of new drugs and novel treatments for patients with schizophrenia or bipolar disorder.

During 2019, our research focused on refining methodology at all levels from molecular tools, to behavioural paradigms for animal and patient recordings. With these efforts, we have developed a platform which is applied in different work packages. One highlight of these efforts is the recently published work by Maki-Marttunen and co-workers (2019). Here, they expand on previously developed neuron models (Mäki-Marttunen et al., J Neurosci Methods, 2018) to create a comprehensive network study on genetic effects on a model cortical circuit bringing us one step closer to link gene variants for brain function.

The DigiBrain project is a true transdisciplinarity effort where mathematical models are designed to explain experimental data, predict novel experiments, and assist in explaining what is being measured. Mathematical models have explained how combinations of identified gene variants may contribute to observed changes in brain activity as measured with EEG. Transdisciplinarity is the only way to reveal mechanisms linking gene variants to brain function.

We believe that the DigiBrain project creates value by bringing novel insight into disease mechanisms, a fundamental understanding of what is measured by EEG, development of molecular biology tools and, not at least, by training the next generation of researchers with generic skills in working across disciplines.

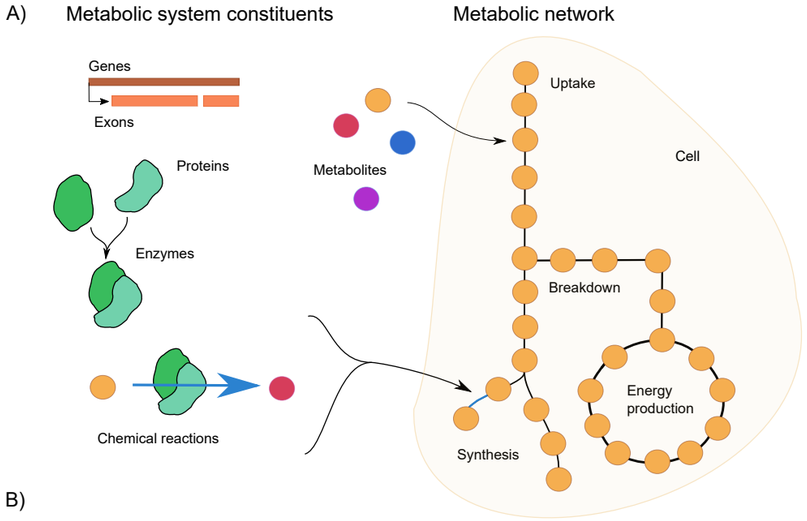


Figure: Marie Gulla

Computer models of salmon's metabolic reaction network (A) are evaluated using the Memote toolkit for metabolic model testing (B). The test suite checks whether the model can perform the same functions as real salmon, e.g. building up or breaking down particular molecules. Thus we can document the current capabilities of our model (B, left) and compare model versions (B, right).

DigiSal

- from a reactive to pre-emptive research strategy in aquaculture

PROJECT LEADER: JON OLAV VIK **INSTITUTION:** NORWEGIAN UNIVERSITY OF LIFE SCIENCES NMBU

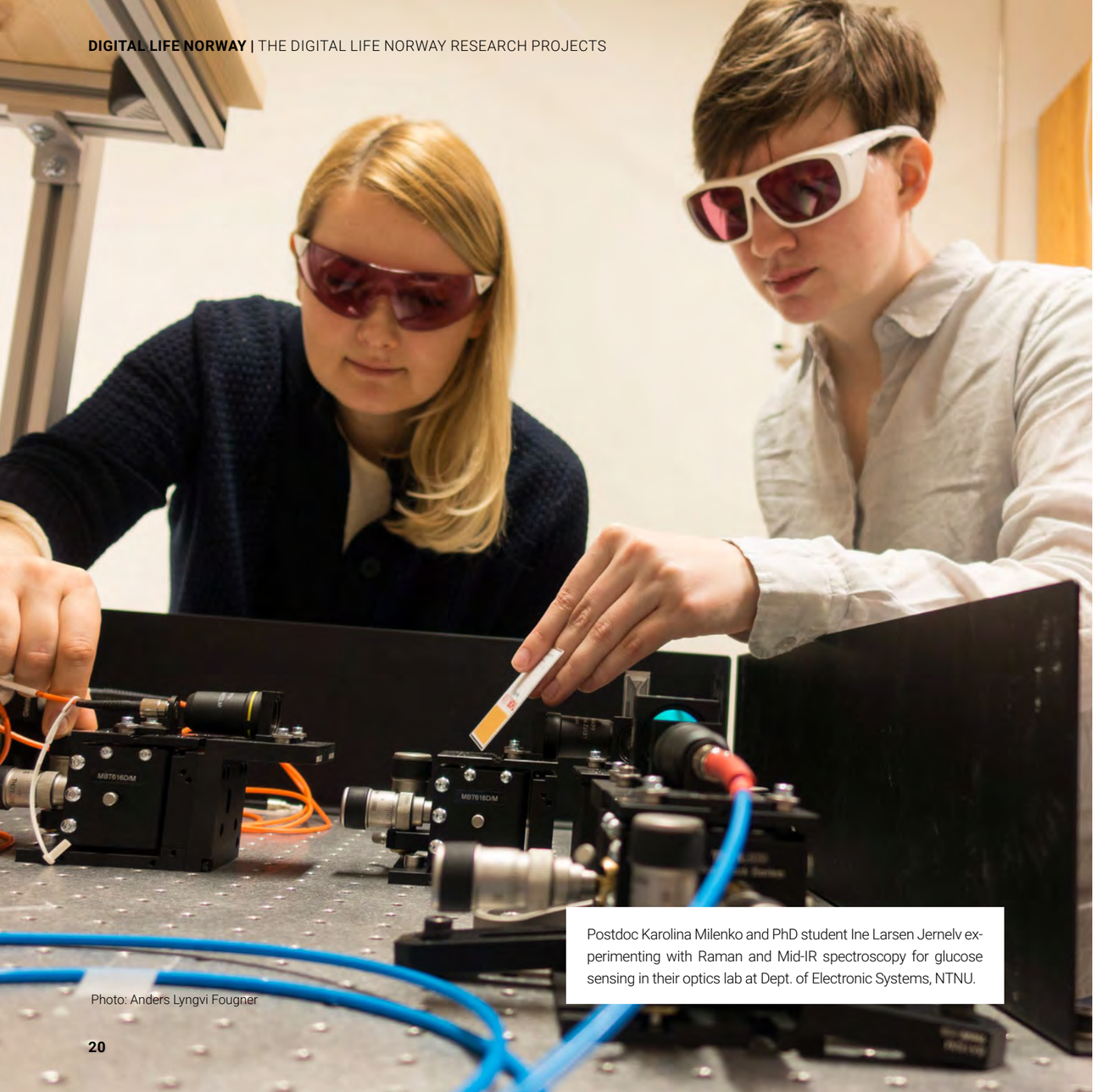
The Digital Salmon uses mathematical modelling to connect and unify data and knowledge about salmon biology. Despite tremendous growth in research and data collection for aquaculture, integrating biological knowledge into the data analysis remains a bottleneck. By translating our knowledge into numbers and equations, we can use computer simulations and the rules of mathematics to deduce new insights and reveal errors or gaps in our understanding. This is a grand endeavour that will require new thinking about biology and business alike, as stakeholders learn to share and reuse data and mathematical models in hitherto unforeseen ways. While the main economic drive comes from aquaculture, the resulting knowledge base will benefit research and management of wild populations of salmon and other salmonids too, as new populations can be placed into the mathematical framework with modest experimental or field effort.

Our research in 2019 has focused on finalizing a core model of the metabolic reaction network of salmon, to be followed by genome-scale and tissue-specific incarnations of the model, providing a novel look at gene expression data from our own experiments and collaborating projects. DigiSal researchers have successfully knocked out genes involved in omega-3 metabolism of salmon, elucidating related biological pathways.

A highlight of 2019 was the first Digital Salmon industry workshop, which achieved a moral commitment from industry, academia and funders to collaborate towards a shared, pre-competitive knowledge base of mathematical models and data on salmon biology. A working group was formed, tasked with developing a white paper and roadmap for generating value from the Digital Salmon knowledge base. On the science side, we contributed to the completion of a scientific community standard for testing and documenting metabolic models together with many other research groups. This is vital for the future maintenance, refinement, and critical evaluation of metabolic models as we apply them for instance to optimize feeds based on novel, sustainable feedstuffs.

Transdisciplinarity is at the heart of systems biology and mathematical modelling, as the formulation of a mathematical model makes clear what a family of systems have in common (the form of the mathematical equations or computer program) but also how they differ (in their respective parameter values or settings for a computer simulation). Discussions between biologists, lab technicians, mathematicians, and businesspeople become more concrete when the mechanisms underlying a phenomenon of interest are formulated in terms of real-world, observable quantities. This helps clarify, for instance, which data are needed to answer a given biological question, or how to design an experiment to decide between possible explanations of a phenomenon.

The Digital Salmon aims to be valuable not only to the aquaculture industry but also to wildlife research and management. In 2019 we initiated dialogue with a social-science project studying the interaction between different user groups of salmon river systems, and also with the Digital Life project Res Publica, on the equitable sharing of value produced from digital life biotechnology. Openness, reproducibility, sharing and reuse of models and data are cornerstones for enabling trust in data and modelling analyses so that it becomes a political question what to do with the resulting knowledge.



Postdoc Karolina Milenko and PhD student Ine Larsen Jernelv experimenting with Raman and Mid-IR spectroscopy for glucose sensing in their optics lab at Dept. of Electronic Systems, NTNU.

Photo: Anders Lyngvi Fougner

Double Intraperitoneal Artificial Pancreas (DIAP)

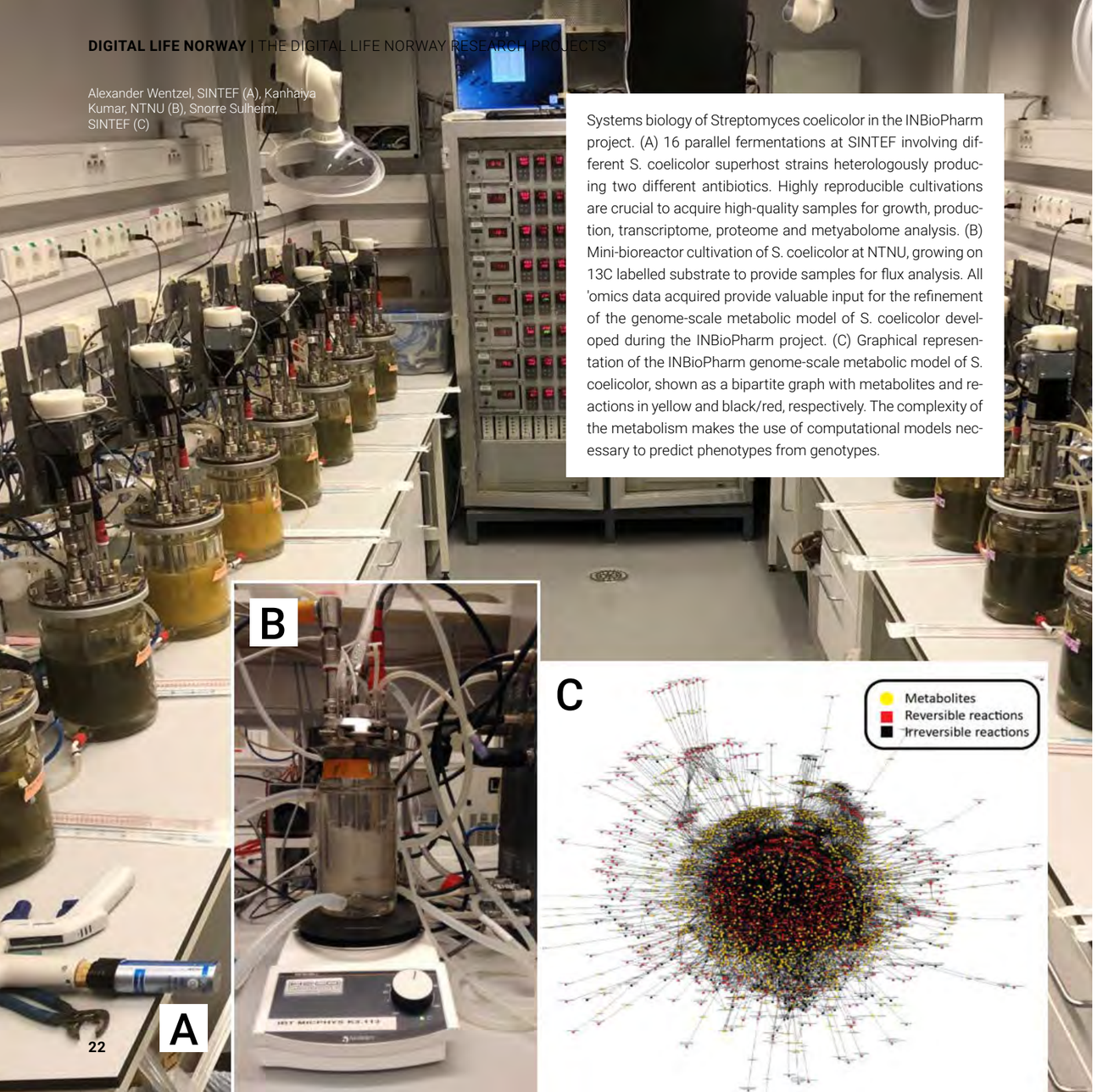
PROJECT LEADER: SVEN M. CARLSEN **INSTITUTION:** NORWEGIAN UNIVERSITY OF SCIENCE AND TECHNOLOGY NTNU

We are making an artificial pancreas, a fully automated system that can deliver insulin to patients with diabetes type 1, that normalizes or close to normalizes glucose levels. This will relieve the patients from their daily need to focus on glucose levels and adjusting insulin boluses. More importantly, an effective articficial pancreas may eradicate the long-term adverse effects of diabetes and normalize life expectancy.

During 2019, our research focused on animal studies of the effect on glucose homeostasis by intraperitoneal insulin and glucagon delivery. In a series of animal experiments, we explored the glucose effect by repeated micro-boluses of glucagon. Further, we worked to develop new technology for measuring intraperitoneal glucose levels.

In the animal experiments, we showed that repeated micro-boluses of glucagon can protect against hypoglycemia. This might be a clue to make our artificial pancreas with "perfect" glucose control. We also achieved some very promising preliminary results in intraperitoneal glucose sensing.

We are working in the cross-roads between technology, biology, and medicine. Only by combining expertise from physics, electronics, cybernetics, biology, and veterinary and human medicine we will be able to implement our ambitious artificial pancreas project. We think that our project creates value for patients, Norwegian medtech industry and the society at large because patients with type 1 diabetes will achieve an easier everyday life without the continuous need to focus on their glucose levels and adjustment of insulin delivery. They will also no more have to worry about long-term adverse effects of having diabetes, and their life expectancy will no longer be reduced by having diabetes. The society at large will save health care and sick leave spending and it will be a welcome opportunity for Norwegian medtech industry.



Alexander Wentzel, SINTEF (A), Kanhaiya Kumar, NTNU (B), Snorre Sulheim, SINTEF (C)

Systems biology of Streptomyces coelicolor in the INBioPharm project. (A) 16 parallel fermentations at SINTEF involving different S. coelicolor superhost strains heterologously producing two different antibiotics. Highly reproducible cultivations are crucial to acquire high-quality samples for growth, production, transcriptome, proteome and metyabolome analysis. (B) Mini-bioreactor cultivation of S. coelicolor at NTNU, growing on 13C labelled substrate to provide samples for flux analysis. All 'omics data acquired provide valuable input for the refinement of the genome-scale metabolic model of S. coelicolor developed during the INBioPharm project. (C) Graphical representation of the INBioPharm genome-scale metabolic model of S. coelicolor, shown as a bipartite graph with metabolites and reactions in yellow and black/red, respectively. The complexity of the metabolism makes the use of computational models necessary to predict phenotypes from genotypes.

INBioPharm

- Integrated novel natural product discovery and production platform for accelerated biopharmaceutical innovation from microbial biodiversity

PROJECT LEADER: ALEXANDER WENTZEL **INSTITUTION:** SINTEF

The INBioPharm project is developing an innovative platform for more efficient discovery of novel antimicrobial drugs. The starting point is a large strain collection of Actinobacteria collected from the Trondheim fjord. We are combining new bioinformatics, cloning, synthetic biology, and screening tools to find and express promising biosynthetic gene clusters (BGCs) from these strains and characterize new bioactive compounds encoded in them.

In 2019, the different components of the INBioPharm biodiscovery platform were refined, integrated, and applied to validate their applicability. Our bioinformatics pipeline has been used once more to extract an additional set of highly promising BGCs for direct cloning by our US collaborators at Varigen Biosciences Corp. This will bring our portfolio to include nearly 50 different highly promising novel and model BGCs for expression in our panel of optimized Streptomyces coelicolor host strains. After conclusion of ERASysAPP project SYSTERACT in June 2019, further systems-scale characterization of these strains has continued in INBioPharm. We developed new metabolomics protocols to study primary metabolism and precursor supply in detail and we launched an updated metabolic model of S. coelicolor as a community model hosted on GitHub for further development by all research groups working on this organism. By optimizing the conjugation procedure applied to introduce cloned BGCs into S. coelicolor, we addressed a key bottleneck in high throughput expression of cloned BGCs in multiple host strains. In 2020, the final year of the project, we will focus on demonstrating the full functionality of the INBioPharm biodiscovery platform and disseminating the diverse project results in both high-ranking scientific journals and to the wider public.

Specific highlights of our work in 2019 include the successful heterologous production of an antibiotic compound in S. coelicolor based on its 130 kb direct-cloned BGC from its natural producer strain. This clearly demonstrates the power of the new cloning technology developed by Varigen in combination with our method to transfer large BGCs into S. coelicolor. We presented our results at multiple international conferences in Norway, Europe, USA and Mexico, including the Functional Metagenomics 2019 conference in Trondheim in June. In connection with the latter and as an important add-on to the INBioPharm project, the INTPART project NORUSCASA was launched, expanding our discovery efforts directly to environmental metagenomes and our network to include additional strong partners in Canada and South Africa. In addition, the new project adds a strong educational component for the next generation of scientists highly skilled in the field of functional metagenomics for novel bioactive natural product discovery.

Education and dialogue with students, policy makers, and the wider public about bioprospecting for antibiotics and their current use in the light of further emerging antimicrobial resistance are an important part of our understanding of transdisciplinarity. To expand on this aspect, we started planning several new events in 2020 that address these topics in close collaboration with the other antibiotics focused projects in DLN, project Res Publica, and the DLN Centre project itself. With this, we think that our project will deliver added value on the broadest possible basis, not just limited to our primary goal to accelerate biopharmaceutical innovation and satisfying pressing medical needs.

Photo: Geir Mogen

The Electron Beam Lithography (EBL) equipment at the NTNU Nanolab is crucial equipment for research and development of the photonic sensors.

Lab-on-a-chip

- biophotonic sensor platform for diagnostics

PROJECT LEADER: ASTRID AKSNES **INSTITUTION:** NORWEGIAN UNIVERSITY OF SCIENCE AND TECHNOLOGY NTNU

The purpose of the project is to develop a generic, lab-on-a-chip (LOC), label-free sensor platform capable of performing highly sensitive and selective multiplexed quantitative diagnostic tests. LOC technology has unique characteristics that enables fast, low-cost analysis for point-of care and in-home testing. Early and reliable detection of disease biomarkers dramatically increases the chance for successful treatment.

Work is underway to develop a tiny laboratory —about the size of a postage stamp— that can analyze patient samples quickly and accurately. Tiny amounts of sample fluid are transported to the sensors using microfluidic channels. By modifying the surface functionalization of the multiplexed photonic sensing elements, the LOC can detect different biomarkers in parallel to achieve a limit- of-detection (LOD) in the ng/ml to pg/ml range. This has numerous potential biomedical applications from diagnosing infectious diseases to cancer detection.

During 2019 our research focused on stabilizing the surface functionalization, developing new sensor designs to improve the LOD, and developing new protocols for fabrication of polymer microfluidics to enable upscaling. These new polymers are hydrophilic, cure quickly at low temperatures, and have low solvent permeability, giving them an advantage over the old polymers. We developed simulation models to study the mass transport of the analyte in order to provide efficient transport to the sensor surface and designed and characterized a herringbone micromixer and other micro-/nano-structure configurations. Our novel sensor design enabling efficient multiplexing, low LOD, and large dynamic range is being considered for a patent in collaboration with NTNU TTO.

We have produced multi-channel chips to enable multi-analyte sensing. In the current design, different analytes are measured in different channels, and each channel is read out separately. Different physiological concentrations of the biomarker C-reactive protein (CRP) have been measured and the specified detection limit reached (<5 ug/ml).

In 2019, we developed two new sensor designs that further improve the LOD so that we can measure targets on the order of ug-ng /ml. We are close to achieving the targeted LOD for the biomarker lipocalin-2 (LCN2), a biomarker for kidney injury. To achieve the sensitivity necessary to measure physiologically relevant concentrations of tumor necrosis factor (TNF), we will likely use amplification.

By transdisciplinarity we understand that many disciplinary boundaries are crossed, and concepts and models from one field can be successfully applied to others to create a holistic approach. Our project team represents the fields of biology, physics, photonics, nanotechnology, microfluidics and medicine. Transdisciplinarity is important to our project because we must collaborate closely between the different fields to achieve the goals of the project.

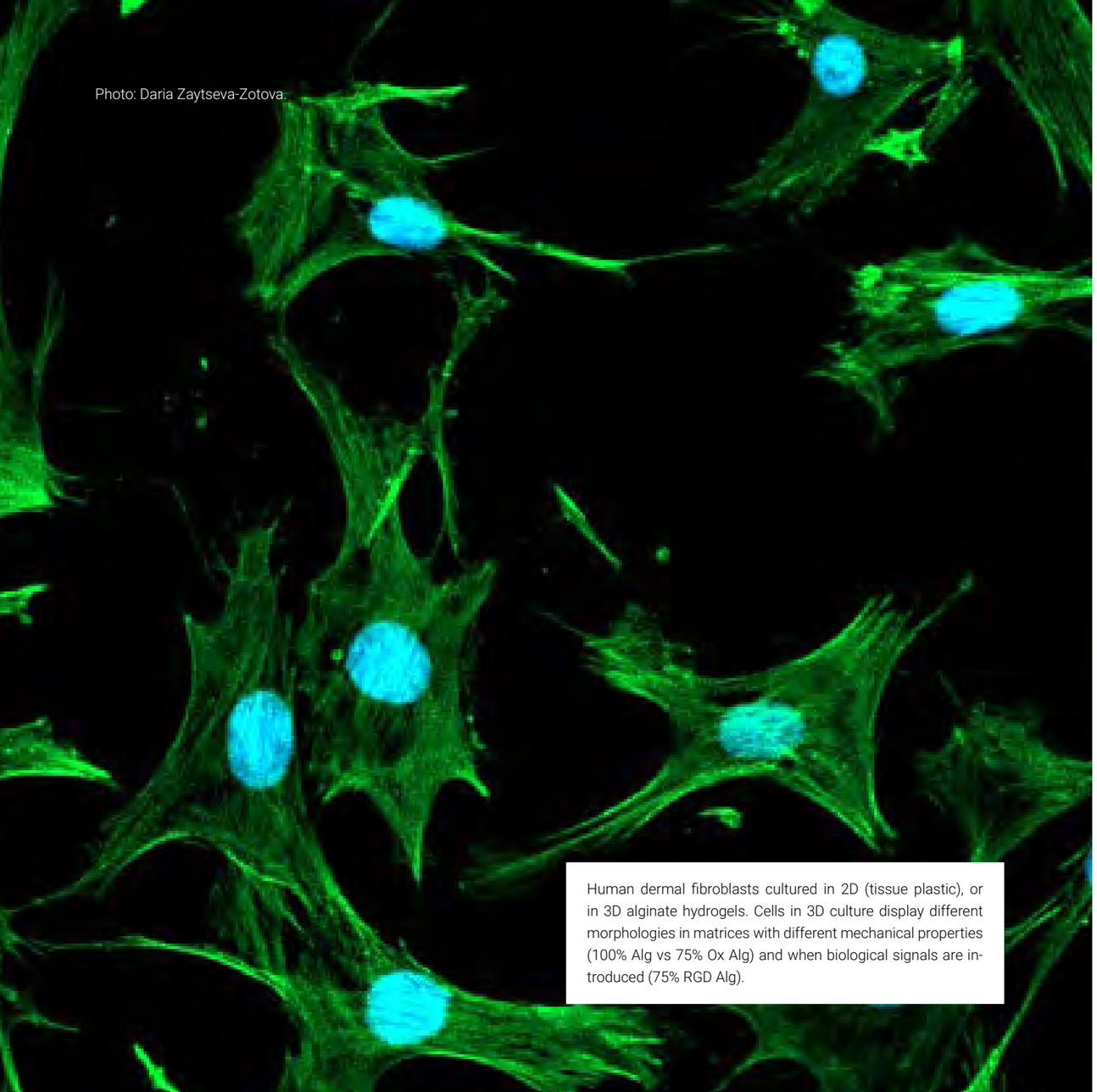


Photo: Daria Zaytseva-Zotova.

Human dermal fibroblasts cultured in 2D (tissue plastic), or in 3D alginate hydrogels. Cells in 3D culture display different morphologies in matrices with different mechanical properties (100% Alg vs 75% Ox Alg) and when biological signals are introduced (75% RGD Alg).

3Dlife

- Emulating life in 3D with digital and experimental tissue models

PROJECT LEADER: BERIT LØKENSGARD STRAND **INSTITUTION:** NORWEGIAN UNIVERSITY OF SCIENCE AND TECHNOLOGY NTNU

The purpose of the project is to develop experimental and digital 3D tissue models. 3DLife aims to discover novel strategies for microtissue engineering in 3D to provide model systems of tissue function and bridge the gap to ***in vivo*** conditions. For the experimental models, we use hydrogel systems with tailorable mechanical and biological properties, and fibroblasts that are essential for the creation of tissue structures ***in vivo***.

During 2019, our research focused on culture conditions and method development for investigating different fibroblasts in our hydrogel systems in order to perform a pilot study on RNA screening. We have investigated a total of six different fibroblast cell lines that show differences in their ability to proliferate in regular 2D culture (on tissue treated plastics). Initial responses to different chemically modified alginates were evaluated for cell attachment on top of alginate gels (2D culture). Two fibroblast cell lines were tested in 3D culture. Both human lung fibroblast (IMR90) and human dermal fibroblasts (HDF) changed morphology when a peptide containing the amino acids Arginine (R), Glycine (G), and Aspartic acid (D), known from the extracellular matrix (RGD-peptide), was introduced to the materials.

One highlight of 2019 has been showing clear differences in morphology of fibroblasts (HDF) in 2D and some different 3D hydrogels (see attached picture). This was the basis for performing a pilot RNA screening of the cells to unravel differences in molecular expression patterns between the cells under different culturing conditions.

In our project, transdisciplinarity is shown by competence in cell biology, chemistry, hydrogels, robotics, statistics, and social sciences. This is important to our project because the difference competences contribute different things to planning experiments, data analysis, RRI work, and learning how to work together as a team.

We think that our project creates value for the scientific community and may also be valuable to medicine, health, and industry. We are creating knowledge about cell responses to biomaterials and cell behavior under different culturing conditions and methods for the handling of cells in 3D culture. We aim to develop tissue structures that are useful to both the scientific community and industry for studying tissue biology, disease progression, and for testing pharmaceutic and toxic compounds.

Extracting a sample from a lab scale bioreactor used to cultivate lipid accumulating thraustochytrids. Conditions like pH, oxygen level, temperature are carefully controlled and the growth performance can be monitored precisely with online detectors. The red colour is from the carotenoid astaxanthin, a bi product added to salmon feed to give the fish its colour red.

Photo: SINTEF

AurOmega

- Microbial production of Omega-3 fatty acids

PROJECT LEADER: PER BRUHEIM **INSTITUTION:** NORWEGIAN UNIVERSITY OF SCIENCE AND TECHNOLOGY NTNU

AurOmega addresses a factor in the demand for increased salmon farming: the need for new sources of omega 3 fatty acids. Salmon farming is economically important for Norway, and an increased and sustainable food production is important for an increasing global population.

The purpose of our project is to obtain increased knowledge of the biosynthesis of the omega-3 fatty acid DHA in the marine organisms, thraustochytrids. Thraustochytrids can be cultivated at high cell concentrations and are extremely promising microorganisms for development of an economically competitive production processes of omega-3 fatty acids. However, yields and productivities are still too low to compete commercially against traditional DHA raw material sources as fish oil, and more basic knowledge about DHA biosynthesis and lipid accumulation is needed.

During 2019 our research focused on three main areas: 1) the metabolic model for the organism was refined and validated, 2) standard protocols for cultivations with defined media and sampling for quantitative PCR, proteome and metabolite analyses were established, and 3) mass spectrometry based methods for NAD, CoA, free-fatty acids and lipids were set up in the lab and adapted to thraustochytrid cells at different growth stages. In addition, we worked on establishing methods for gene transfer.

A highlight of 2019 was publishing the first scientific paper from the project in Scientific Reports . We participated in the 1st International Conference on Labyrinthulean Protists (ICoLP) in Japan. This allowed us to make contact with all important groups working on these organisms worldwide. Visits to other labs by AurOmega team members will happen in 2020.

By transdisciplinarity we understand that researchers from several different disciplines are working together with one common goal. In Auromega, researchers with experience from the fields of synthetic biology, systems biology, bioprocess technology, and mathematical modelling are needed in order to reach our goal. We meet regularly to ensure that everyone knows the challenges the other researchers are facing and can contribute with their knowledge to aid in solving those challenges. It is only through this transdisciplinary approach we can achieve the ambitious goals of AurOmega.

Photo: J. Zehner.

Leica confocal laser microscope used by Jennifer Zehner in her PhD work.

BioZEment 2.0

- Systems analysis and fundamental control of bacterial processes in the production of bio-concrete for construction purposes

PROJECT LEADER: ANJA RØYNE **INSTITUTION:** UNIVERSITY OF OSLO

The purpose of the project is to develop a more sustainable alternative to conventional concrete through the use of naturally occurring mineral-microbe interactions. The production of concrete currently accounts for more than 5% of global anthropogenic CO2 emissions, and radical new methods and materials are needed to reduce greenhouse gas emissions from the construction sector.

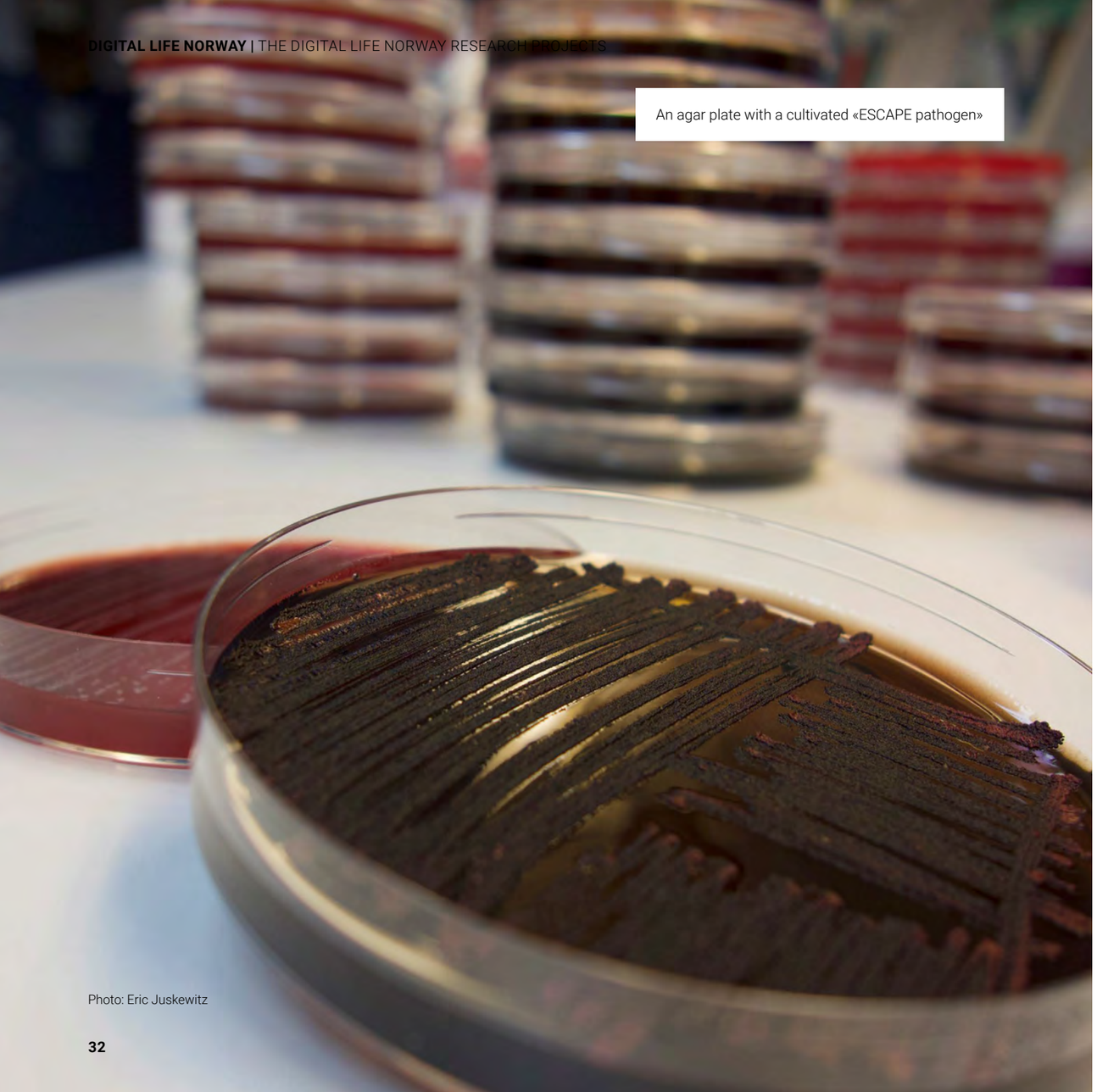
The BioZEment concept is based on the dissolution and precipitation of calcium carbonate by selected non-pathogenic bacterial strains. Our ambition in this project is to combine systems biology metabolic modeling of bacterial strains, advanced microbiological techniques, material characterization, and 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 are also investigating the regulatory, environmental and consumer aspects that may influence the future use of the product.

During 2019, our research focused on refining models and experimental methods, and generating experimental data for integration with our computational models. We have resolved a long-standing challenge in the cultivation of our strains and performed fermentation experiments that will provide critical input to the systems biology modeling. The geochemical reactive transport simulations have been benchmarked against existing experiments and the microscale experiments are now running well and generating data to be further integrated with the geochemical model.

One highlight of 2019 has be en the publication of two transdisciplinary companion articles in PLOS One, co-authored by several researchers from this project. In particular, the article *Towards a low CO2 emission building material employing bacterial metabolism (2/2): Prospects for global warming potential reduction in the concrete industry* (Myhr et al, 2019) has received significant attention from readers due to its novel, integrated approach to cost, emissions reductions, and market potential. These results serve as important background information for the consortium to prioritize between possible alternative directions of the project.

Our research is transdisciplinary. Different disciplines not only work in parallel, but project participants from different disciplines are able to interact, understand each other, and influence each other's work. This is important to our project because we aim to tackle challenges that cannot be solved within individual disciplines alone. For instance, we have one PhD student who works on modeling but also takes active part in microbiology experiments. This allows for much better integration of experimental and modeling approaches.

Our project creates value for the biotechnology research field, particularly the nascent field of construction biotechnology. We are developing new, integrated methods and understanding that can be applied to several emerging problems. In order to maximize value creation, we focus on the innovation and open data aspects of our project in close collaboration with the DLN network.



An agar plate with a cultivated «ESCAPE pathogen»

Photo: Eric Juskewitz

DigiBiotics

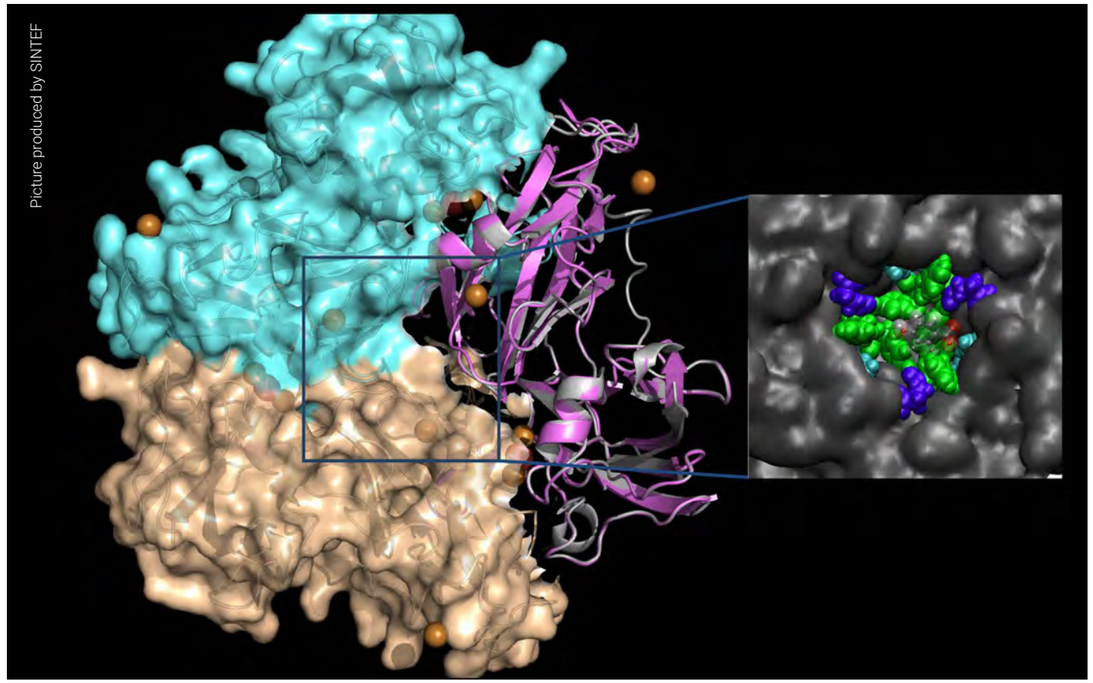
- Digital discovery of antimicrobial molecules from marine Arctic resources with reduced risk of triggering resistance

PROJECT LEADER: JOHN-SIGURD MJØEN SVENDSEN **INSTITUTION:** UNIVERSITY OF TROMSØ

An important cause of the global antimicrobial resistance crisis is the lack of new and effective antibiotics. The are many reasons for the lack of new drugs, but insufficient tools and workflows needed to investigate new chemical space for the discovery of new molecules is an important one.

The purpose of DigiBiotics is to create enabling technologies that provide access to new molecular classes that have, until now, been unattractive to the pharmaceutical industry. An important milestone for DigiBiotics is the validation of its technologies through the discovery of novel antimicrobial molecules from marine biodiscovery.

DigiBiotics is still a young project. Our first year was focused on establishing the different work-packages, and in 2019 the work-packages started to interact to create the complete DigiBiotics pipeline. The pinnacle event of 2019 was when the first molecules designed and created by Digibiotics were investigated in our membrane models from a theoretical and experimental perspective. These molecules showed antimicrobial efficacy in patient-like models. This achievement is a proof of concept for DigiBiotics, and the foundation upon which research over the next several years will be built.



Three-dimensional model of a newly identified multicopper oxidase (pink), superimposed on one of the monomers of the crystal structure of the trimeric small laccase from Streptomyces viridosporus T7A (PDB code: 3TAS) (the monomer used for superposition is grey; two other monomers, shown with surface, are blue and light brown; copper atoms are shown as brown sphere). The picture to the right shows details of the Cu T1 site with a model substrate.

OXYMOD

- Optimized oxidative enzyme systems for efficient conversion of lignocellulose to valuable products

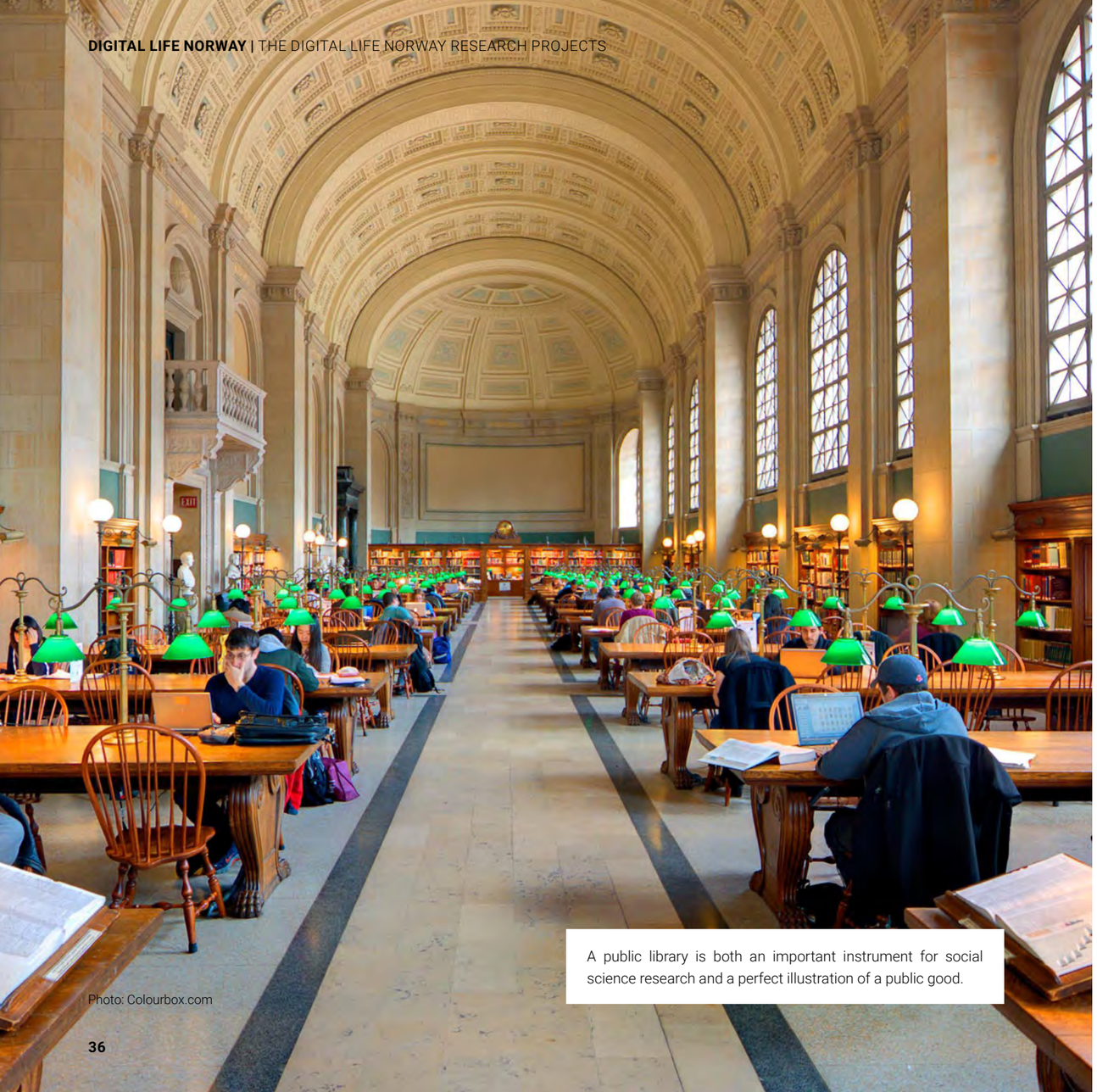
PROJECT LEADER: VINCENT EIJSINK **INSTITUTION:** NORWEGIAN UNIVERSITY OF LIFE SCIENCES NMBU

OXYMOD aims to discover, understand, and apply redox enzyme systems to the conversion of biomass, such as lignocellulose, into valuable products. OXYMOD is combining expertise from life sciences (enzyme technology, microbial biotechnology, high throughput screening, advanced analytics), bioinformatics (big data, enzyme systems modelling, process modelling) and engineering (enzyme evolution, synthetic biology) to develop novel biocatalytic systems.

After mining 1000 Actinomycete genomes, the work in 2019 focused on producing and characterizing novel enzymes, in particular: multicopper oxidases and peroxidases acting on lignin, lytic polysaccharide monooxygenases (LPMOs) acting on cellulose or chitin, and enzymes that may be involved in the channeling of the electrons and/or transition metals that are central in these redox enzyme systems. Concomitantly, we have initiated both modelling and experimental assessment of kinetics, structural dynamics, and catalysis for individual enzymes and made our first steps towards kinetic modelling of complete enzyme systems.

Highlights of 2019, include identification of new multicopper oxidases and peroxidases that are active against lignin-derived compounds, novel insights into LPMO catalysis, and the generation of atom-scale models of multicopper oxidases. A major milestone was the publication of a paper in which the mass spectrometry-based high-throughput screening facilities at SINTEF were successfully used to change the properties of an LPMO acting on cellulose and chitin. Much progress has been made in developing this technology for the optimization of enzymes acting on lignin. Through collaboration, we obtained the first insight into the interplay between (lignin-active) laccases and (cellulose-active) LPMOs.

Our interdisciplinary approach – combining techniques from different knowledge domains such as big data mining, atom-scale modelling, molecular biology, biochemical protein characterization, and robotic variant screening provides a unique possibility to further our understanding of enzyme systems for the degradation of lignocellulosic biomass and to create bioeconomic value in Norway. The project has multiple direct and indirect links to multiple industries and technologies developed by OxyMod partners are already used in industrial settings.



A public library is both an important instrument for social science research and a perfect illustration of a public good.

Photo: Colourbox.com

Res Publica

- Responsibility, practice and the public good across Digital Life

PROJECT LEADER: HEIDRUN ÅM **INSTITUTION:** NORWEGIAN UNIVERSITY OF SCIENCE AND TECHNOLOGY NTNU

The purpose of the Res Publica project is to study the distribution of responsibilities for creating public good from public research investments. We investigate the relations between the biotechnology research conducted within Centre for Digital Life Norway (DLN) and its socio-economic-political context. We aim to identify the entangled dynamics of social responsibility, as well as sites and issues where responsibility measures are needed.

During 2019, our research focused on how DLN implements innovation policies, and on institutional issues concerning DLN's positioning in the Norwegian research landscape. In addition, we researched the governance of farmed salmon, bioprospecting, and antimicrobial resistance.

By transdisciplinarity, we understand a problem-oriented research approach that is focused on solving societal challenges and that draws on experience-based knowledge of relevant societal actors in the research process. This is important to Res Publica because we refined our research strategies to the topical areas we identified in our screening of DLN-projects during the first project year (governance of salmon, bioprospecting, and antimicrobial resistance).

Res Publica creates value for the Norwegian biotechnology community, funding agencies, policy developers, social sciences, and the public by generating new knowledge and reflection about societal issues of a research center like DLN. Our results can improve DLN activities and policy development by identifying tensions among contradictory policy demands, academic work conditions, and value distribution.

Photo: Colourbox

AHA!

– Adaptive Heuristics and Architecture

PROJECT LEADER: JARL GISKE **INSTITUTION:** UNIVERSITY OF BERGEN

AHA! is a transdisciplinary project focusing on bridging the rather isolated traditions of physiology and ecology to develop a model of animal decision-making, stress, and wellbeing. We have developed a modularized general model of a population of animals with behavioral architecture based on the architectures evolved for handling and responding to information from the environment and the body. We exposed these virtual organisms to standard ecological and environmental scenarios to test the importance of each module component for the emergence of behavioral strategies, personality types, and physiological/behavioral syndromes. One highlight of 2019 has been the publication of a general model for the cognitive process of decision-making in animals.

During 2019, we incorporated hormonal dynamics into our models of optimal behavior. This will lead to submission of 2 PhD theses in early 2020. We have also extended the general model for decision-making to cover important aspects of stress and wellbeing in fish and other animals. We think that, in the long-term, our project will create value for aquaculture and other animal production industries by helping them respond to the public expectation and demand for transparent and evidence-based information about ethical food production.

Photo: Lars A. Akslen/CCBIO
Copyright: CCBIO

The HyperionTM Imaging System is a high-dimensional imaging system capable of analysing 4 to 37 protein markers at subcellular resolution and localization in fixed tissue sections or cell smears. With the ability to utilize up to 135 channels to detect additional parameters, the Hyperion Imaging System is ideal to model the complex tissue landscapes in malignant tumours and to meet researcher needs today and well into the future.

Centre for Cancer Biomarkers (CCBIO)

PROJECT LEADER: LARS A. AKSLEN **INSTITUTION:** UNIVERSITY OF BERGEN

CCBIO focuses on the interaction between tumour cells and their surrounding microenvironment to better understand cancer biology, increase diagnostic precision, and improve targeted cancer treatment. We are working hard to discover, validate, and apply biomarkers in a cost-effective and socially responsible way.

During 2019, CCBIO have reported how cancer cells program their microenvironment to make tumours more aggressive. We found that signal pathways regulated by proteins like Axl, Nestin, Prosaposin, and Stathmin are involved in processes that, among other effects, influence immune responses to tumours. Using new imaging mass cytometry technology that we have established, we performed multidimensional characterization of protein markers and their locations in tumour tissues, mapping the complex microenvironment around tumour cells more precisely than before. We can correlate the data with tumour behaviour and patients' response to treatments using our new bioinformatic analysis methods. We have organized a number of clinical studies based on these new methods using innovative biomarker analysis programs (anti-Axl; cryo-immunotherapy; single-cell protein markers and adaptive therapy; liquid biopsies).

CCBIO has extensive international collaborations and an "international faculty" with 16 world-leading scientists. By trans-disciplinarity we understand a setting where researchers from different disciplines work together in a deeply integrated manner towards a research question or common goal. In this respect, CCBIO is inherently transdisciplinary as our research approach spans the full translational spectrum supported by bioinformatics, and addresses ethical and economic aspects of biomarker use in modern cancer- and precision-medicine. CCBIOs unique transdisciplinary approach to cancer is a key feature of attaining its vision.

CCBIO has the only cancer-focused research school in Norway with a comprehensive portfolio of courses, symposia, seminars, thematic meetings, and communication and popularization externally. The actor and cancer researcher Henriette Christie Ertsås, a CCBIO alumna, is collaborating with CCBIO on an education effort aimed especially at children and youths. The most popular play, "Stine Stem Cell," is a free-standing drama adaptation of the book "Biomarkers of the Tumor Microenvironment: Basic Studies and Practical Applications" by Lars A. Akslen and Randolph Watnick (editors).

In 2019, there were 55 PhD candidates (67% women) and 20 postdocs (75% women) at CCBIO, with 8 successful defences. As part of this year's annual CCBIO Symposium, which brings both national and international speakers and over 200 participants, Omid Farokhzad gave the Volterra lecture on Translation & Innovation. This talk resulted in several fruitful break out meetings. Preceding the symposium, CCBIO also organized a satellite symposium with more than 90 participants on Deep Tissue Profiling. Several of CCBIO's PIs have received awards, and many are members of the Norwegian Academy of Science and Letters.

A Biacore T200 instrument which we use for assay development.

Photo: Ruth Brenk

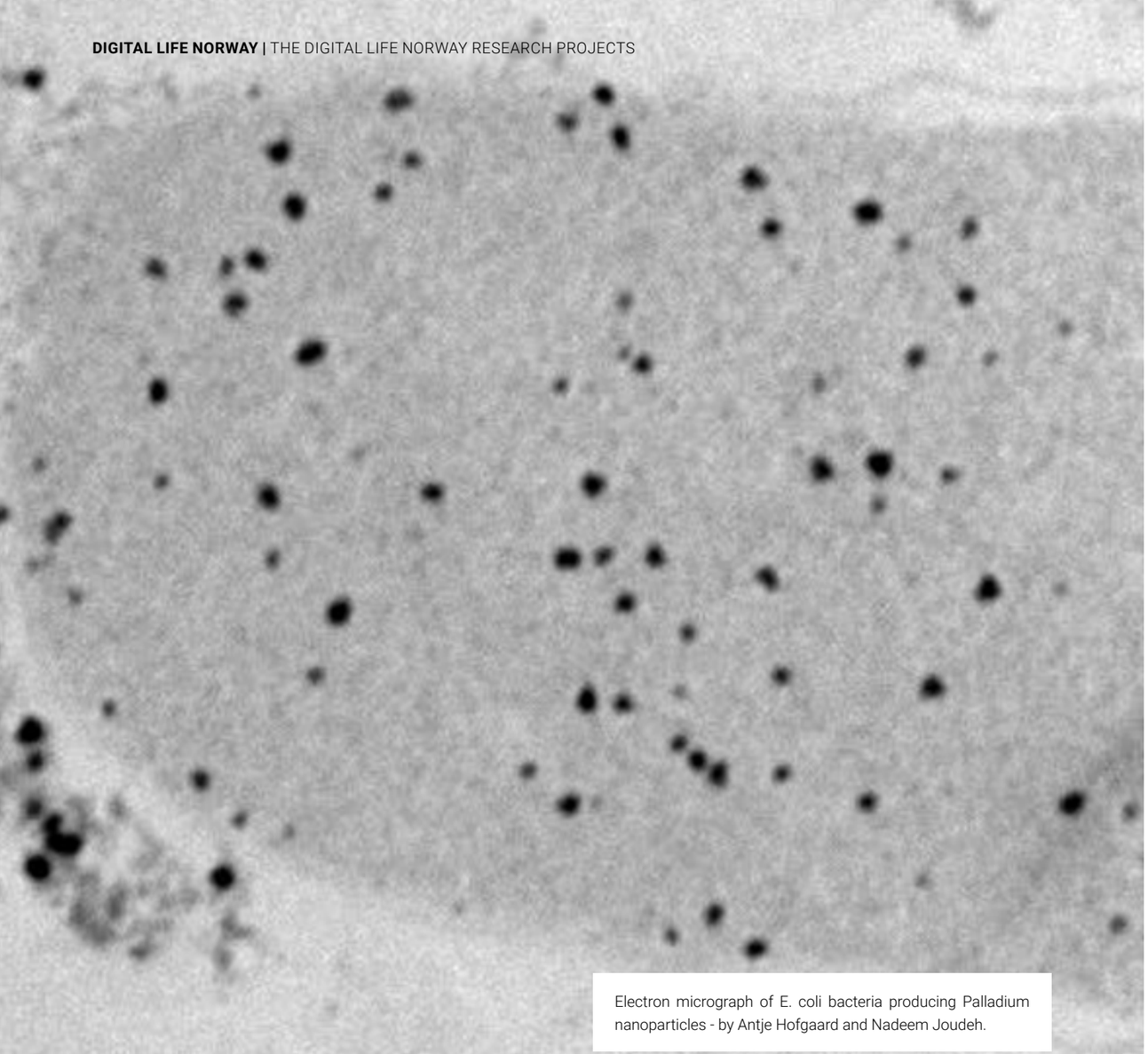
Future antibiotics

- To discover and optimize new antibiotics

PROJECT LEADER: RUTH BRENK **INSTITUTION:** UNIVERSITY OF BERGEN

The purpose of the project is to explore the chemistry of riboswitch ligands and assess their potential as new drug targets for antibiotics. This year, our research has focused on developing a robust assay to determine how ligands bind to riboswitches and to synthesize riboswitch ligands based on computational design. We have also developed a computational method to predict if an RNA binding site is capable of binding drug-like ligands.

In this project, experts in medicinal chemistry, structural biology, biochemistry, and cheminformatics are working together to solve a research problem. If the projects confirms that riboswitches are promising targets for antibiotics, the project will potentially contribute to solving the antibiotic crisis which will be of huge value for the society.



Electron micrograph of E. coli bacteria producing Palladium nanoparticles - by Antje Hofgaard and Nadeem Joudeh.

BEDPAN

- Bio-engineered Palladium nanoparticles

PROJECT LEADER: DIRK LINKE **INSTITUTION:** UNIVERSITY OF OSLO

The purpose of the project is to develop a fully controlled system for producing Palladium (Pd) nanoparticles biologically, with properties that can be fine-tuned by genetic engineering and systems biology principles. This offers a more environmentally friendly way to create materials for use in new and innovative applications of chemical catalysis, medicine, electronics, and energy cells.

During 2019, our research focused on characterizing the genes involved in transporting Pd into E. coli. Different single-gene knockouts where studied and monitored for their ability to transport Pd and produce Pd nanoparticles. We are also carrying out protein purification and crystallization experiments of proteins involved in Pd transport. One of the most interesting properties of our biologically produced Pd nanoparticles is their magnetic moment. This magnetism exists only in a certain nanoscale size regime, and we are currently using complementary methods such as electron paramagnetic resonance to investigate this further.

One highlight of 2019 has been being able to measure the magnetic properties of our nanoparticles by using magnetic force microscopy. This comes after many failed trails in the last three years using different techniques including magnetometers and magneto-optical imaging. The ability to measure and quantify the magnetic moment of our nanoparticles is key to our project because it allows us to track the effect of genetic engineering on the Pd-based materials.

To us, the interaction with possible end users of our technology – industry players from materials science and catalysis is transdisciplinary. Without this input, we cannot succeed in producing materials that are useful to the industry – at the same time, the traditional industry methods for making Pd particles (e.g. for catalysts) do not allow the same level of manipulation that we can achieve with biology.

The value of our technology lies in creating an environmentally friendly alternative method of producing Pd nanoparticles. Conventional chemical and physical methods are expensive, energy-consuming, toxic, and time-consuming. In addition, our ability to genetically engineer the end product properties will allow us to create novel materials for interesting applications in electronics, chemical catalysis, medicine and fuel cell science.

Photo: Colourbox

Listening to the patients

- analysis of body sounds for diagnostics

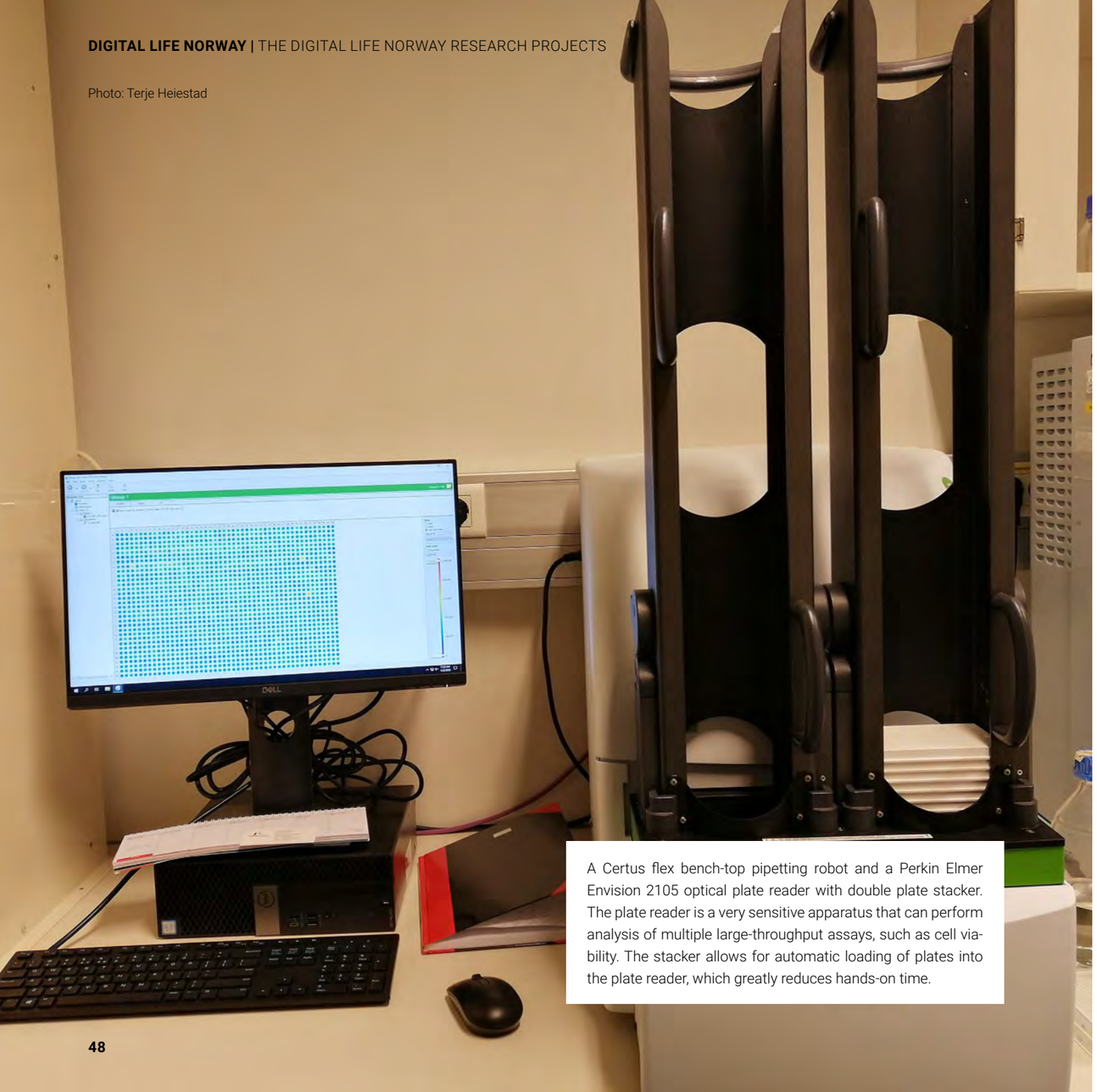
PROJECT LEADER: SVEN M. CARLSEN **INSTITUTION:** NORWEGIAN UNIVERSITY OF SCIENCE AND TECHNOLOGY NTNU

This project is exploring the use of advanced monitoring and processing of abdominal sounds to identify meal intake in patients with diabetes type 1 (DM1) soon after the start of a meal. Identifying meal intake early is essential for delivering the insulin dose needed to keep a patient's glucose levels in the normal or close to normal range. These abdominal sounds may be used by an artificial pancreas to automatically deliver insulin to people with DM1 instead of requiring them to notify the system of a meal. It can also remind or advise people who use manual glucose control about a missed meal bolus.

During 2019, the research focused on identifying optimal sensor locations for collecting abdominal sounds and avoiding contamination by external noise (e.g. from clothing). In a small pilot study this year of 25-30 meals in 15-20 young healthy persons, we were able to identify meal onset very soon after initiation. However, there was a high false-positive rate. In order to use the technology in an artificial pancreas, we need to refine the technology to eliminate false positive meal identifications.

This project combines crucial expertise from physics, cybernetics, electronics, acoustics and medicine to deliver value for patients, the Norwegian medtech industry, and the society at large. Our research will improve quality of life for patients with DM1 by eliminating the constant need to inform the system about every meal in order to manage their glucose levels and insulin delivery. They will no longer have to worry about long-term adverse effects or reduced life expectancy from diabetes. This research will reduce save health care and sick leave costs and it will be a welcome opportunity for Norwegian medtech industry.

Photo: Terje Heiestad



A Certus flex bench-top pipetting robot and a Perkin Elmer Envision 2105 optical plate reader with double plate stacker. The plate reader is a very sensitive apparatus that can perform analysis of multiple large-throughput assays, such as cell viability. The stacker allows for automatic loading of plates into the plate reader, which greatly reduces hands-on time.

PINpOINT

- Pipeline for individually tailoring new treatements in haematological cancers

PROJECT LEADER: JORRIT ENSERINK AND KJETIL TASKÉN **INSTITUTION:** OSLO UNIVERSITY HOSPITAL

PINpOINT is developing a digital pipeline to identify tailored treatments for individual patients with hematological cancer and to model patient outcome using computational predictive tools.

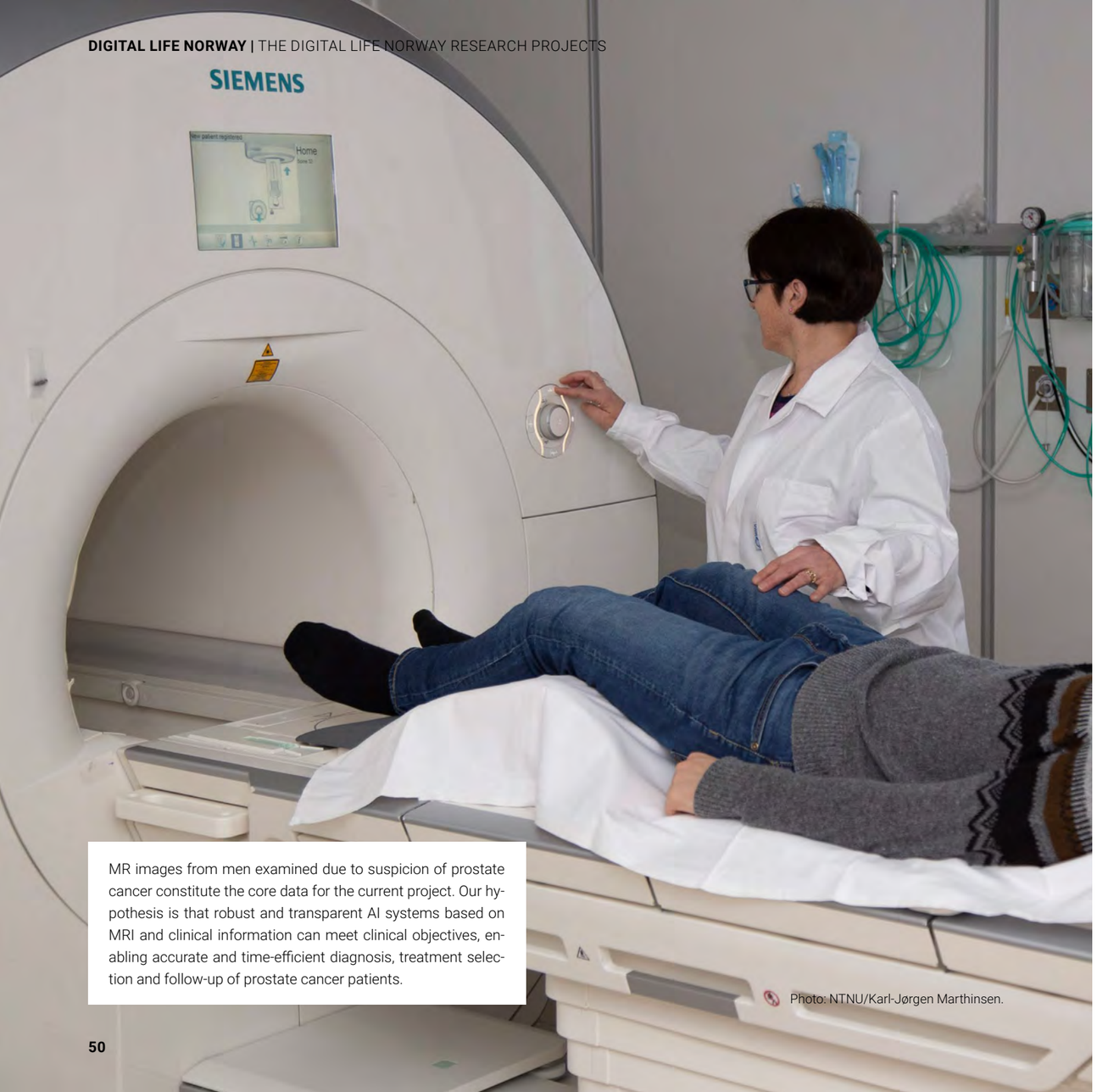
The project started in the second half of 2019 and most of our efforts have focused primarily on laying a solid foundation for the project: recruitment and training of personnel and starting data production using early hired staff and faculty. We have also invested in infrastructure, using funding from Oslo University Hospital and the University of Oslo. With all this in place, the project is well into the data generation phase and we expect data analysis and modelling to start soon.

One highlight of 2019 has been the publication of: Skånland, S.S., Cremaschi, A., Bendiksen, Hermansen, J.U., Govinda Raj, D.B.T., Munthe, L.A., Tjønnfjord, G.E., Taskén, K. (2019) An in vitro assay for biomarker discovery and dose prediction applied to ibrutinib plus venetoclax treatment of CLL. Leukemia, (in press). A paper that reports assays and biomarkers for analysis of drug synergies that can predict optimal dosing of drugs used in CLL.

We are integrating data from leukemia projects with newly developed bioinformatics models to construct a highly innovative digital pipeline. It improves the lives of patients with hematological cancer by advancing tailored therapy, predicting drug synergies and supporting clinical decisions at an individual level. This project also investigates the ethical, legal and regulatory aspects of such a pipeline. Finally, in collaboration with several pharmaceutical companies, we will evaluate the feasibility of using the pipeline in a clinical production setting.

The datasets that we are creating are too large to be analyzed manually; they require transdisciplinary approaches to develop novel modeling and machine learning algorithms. Furthermore, the analysis of primary patient material and the future execution of clinical testing based on the outcome of our drug screens pose legal and regulatory challenges. We will take an interdisciplinary approach to addressing these challenges and the effect they have on individual researchers, research teams, and end-users. The resulting RRI (Responsible Research and Innovation) data will be published through appropriate channels.

Our project creates value for individual patients, their family, and society, by developing new strategies to improve patient outcome. We envision that our project will help patients get treatment with the optimal therapeutics given at the right time and treatment schedule. This may reduce overtreatment of patients and reduce attrition in health care. We also think there may be value and IP in the documentation and development of biomarkers for stratification and in the discovery of novel drug treatments and combinations.



MR images from men examined due to suspicion of prostate cancer constitute the core data for the current project. Our hypothesis is that robust and transparent AI systems based on MRI and clinical information can meet clinical objectives, enabling accurate and time-efficient diagnosis, treatment selection and follow-up of prostate cancer patients.

Photo: NTNU/Karl-Jørgen Marthinsen.

PROVIZ

- Prostate cancer visualization by MRI – improved diagnostics using artificial intelligence

PROJECT LEADER: TONE FROST BATHEN **INSTITUTION:** NORWEGIAN UNIVERSITY OF SCIENCE AND TECHNOLOGY NTNU

PROVIZ is developing an artificial intelligence (AI)-based software to support the detection and characterization of prostate cancer on magnetic resonance (MR) images.

During the past year, we focused on employing the right staff for the project and, importantly, collecting images and clinical variables needed to establish the project's data repository. We are also developing methods for quantitative analysis of MR images to optimize active surveillance schemes for low-risk prostate cancer patients.

Three PhD students and one postdoc joined us in fall 2019. They will work on developing and validating AI algorithms for detection and characterization of prostate cancer, including data standardization to enable inter-patient comparison across multiple centers and scanners. One of the PhDs is solely engaged with the responsible research and innovation (RRI) aspects of the project, exploring the project's development of new technology with AI for prostate cancer diagnostics, as well as its scientific and societal consequences.

A major highlight for 2019 was retrieving the core data for the current project. MR images from 1500 men with suspected prostate cancer examined at St. Olavs Hospital are now anonymized and transferred to HUNT Cloud, a secure server adapted for storage and computational analysis of sensitive data. A reference set of the data is complete with expert segmentations from the radiologist and clinical variables collected from patient journals, and already in use for development of the analytical pipelines of the project.

The project is truly transdisciplinary, integrating expertise from physics, medicine, data science and social science. This is important to our project as the problems we are trying to solve evolved from real-world clinical limitations and are therefore of complex nature.

We think our project creates value for future prostate cancer patients by establishing decision support that will improve treatment outcome, but also for clinicians who will apply the tools, and the health care system in general.

Photo: Colourbox.com

RESPOND3

- Towards better computational approaches and responsible innovation strategies in early drug discovery – application to antibiotics and COPD

PROJECT LEADER: NATHALIE REUTER **INSTITUTION:** UNIVERSITY OF BERGEN

The purpose of this project is to efficiently and responsibly advance two drug discovery projects. The first project aims to discover a new lead for treatment of chronic obstructive pulmonary disease (COPD) and the second aims to find novel antibiotics. To achieve these goals, we will improve and calibrate computational methods for the hit-to-lead and lead optimization steps. Using these two projects as concrete study examples, we aim to propose and implement a model for involving stakeholders and incorporating their suggestions into our research.

RESPOND started in January 2019, and this first year has been mostly dedicated to finalizing a number of formalities and hiring new staff members. Three new staff are already in place and working on various aspects of the project: a chemist, a biochemist, and a molecular modeler have started designing, producing, and testing compounds. A PhD student and a postdoctoral fellow are expected to start later this spring.

In this transdisciplinary project, scientists from widely different but complementary fields —chemistry, biochemistry, biology, computational sciences, and law— are working together to achieve a common goal. To achieve our project aims, it is essential that all staff members understand each other's field, goals, and challenges.

We believe that our project will create value by discovering molecules with a therapeutic potential, which we intend to verify during the project. Beyond this, we hope that the computational methods developed for the project and the model for stakeholder involvement will be useful for drug discovery endeavours in academia.

Photo: Vebjørn Andersson

The centrepiece of our research equipment is the EEG (electroencephalogram) for recording electrical signals originating from the brain. Using a high-density montage of 128 electrodes, and subsequent source estimation of the signals' neural origin, we are able to record relatively precise cortical electrical signals off the outside of the scalp. By applying individual MRI scans and advanced mathematical approaches, we calculate first the signals' origin, and then the individual brain's connectivity network metrics.

AIRDEM

- Assessment of individual risk of dementia in epilepsy: mulitmodal brain based precision prognostics

PROJECT LEADER: IRA HARALDSEN **INSTITUTION:** OSLO UNIVERSITY HOSPITAL

We want to understand cognitive functions through brain development and aging. We aim to contribute to the development of innovative methods for early detection, diagnostic classifications, and treatment evaluation of diverse neurological and neuropsychiatric diseases associated with cognitive health issues. In particular, we focus on how brain network changes, observed with EEG technology, are correlated with cognition and behaviour.

The purpose of our DigitalLife project is to establish a correlation between cognitive decline, synchronisation of brain-originating electrophysiological signals, and neurological disease. To do so, we develop and employ methods to enhance the predictability of EEG by complementing the data with individual MRIs and use advanced algorithms for pattern recognition. The identified patterns are then correlated with cognitive function profiles.

During 2019, we focused on collecting data on patients with focal epilepsy. We have established an interdisciplinary, international research group collaboration that combines different fields of neuroscience and computational science competence to further strengthen our task force for identifying such brain network patterns.

One of the many highlights of 2019 was our research evaluation seminar in Cambridge, where we met with all of our research partners. During innovative discussions, we decided to make a joint application to a European Horizon 2020 call. We believe that to succeed in creating new diagnostic tools in transatlantic competition, it is crucial to focus all collaborative efforts across EU borders and let the creativity and passion from different research cultures reciprocally enhance each other.

Interdisciplinarity means hands-on teamwork across different disciplines to create new research ideas that benefit society. It is important to be both humble and open for new perspectives, knowledge, and research input from different fields of research. A pre-requisite is to communicate and exchange ideas in a way that is relevant for all partners. Each participant must understand the relativity of its own perspective and should not be afraid to open up to new fields and ideas in the creative search for innovative solutions. We think an open-minded, naïve, and child-like approach to meeting with others is crucial for finding new and creative ways of thinking. In our project, we integrate the field of computer science with the fields of clinical medicine and neuroscience.

We hope our project will create value for patient care and clinical diagnostics by understanding how brain networks can be linked to cognitive health. Furthermore, through the use of AI and advanced algorithms, we aim to create a more efficient and insightful use of EEG technology by creating a tool for hospitals to provide better healthcare solutions for their patients.

Parts of the CyTOF mass cytometry instrument used for high dimensional measurements on AML cells.

Photo by Monica Hellesøy.

AML_PM

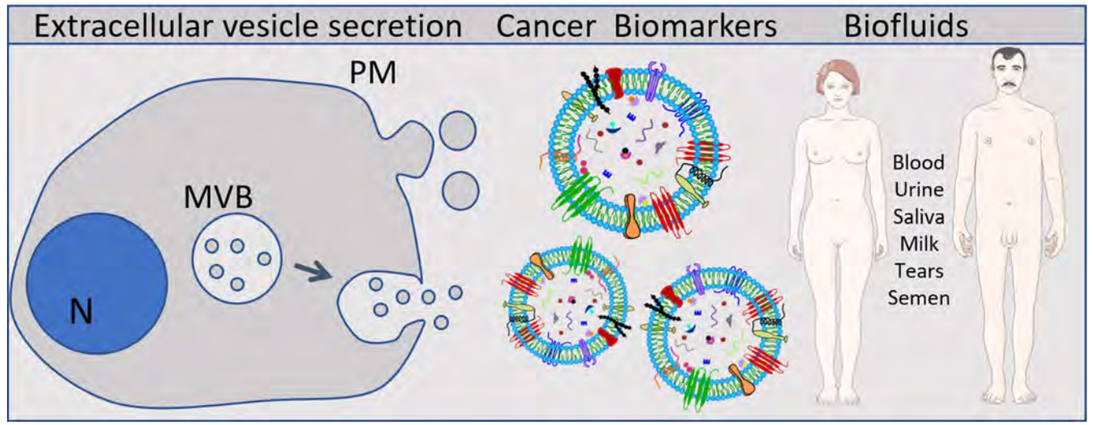
- Improved Treatments of Acute Myeloid Leukaemias by Personalised Medicine

PROJECT LEADER: INGE JONASSEN **INSTITUTION:** UNIVERSITY OF BERGEN

Acute myeloid leukaemia (AML) is a highly aggressive cancer with few treatment options for the majority of patients. Since alterations in cell signalling are a hallmark of the cancer, drugs targeting signalling pathways are being developed. A major challenge is the inter- and intra-tumour heterogeneity of AML patients. The dynamic development of cancer subclones makes it difficult to provide appropriate treatment options. AML_PM is created to address these challenges.

In this project, we pursue a transdisciplinary approach involving clinicians, cell and animal model systems, bioinformatics, and mathematical modelling. The translational approach, with access to AML biobanks as well as longitudinal data from clinical trials, provides a high quality source for big data analytics and mathematical modelling. It includes the implementation of data management to ensure interoperability, reusability, patient security, and outreach to patient organisations and public.

The project is funded by ERA PerMed and involves partners in Germany (DKFZ & University of Freiburg), the Netherlands (University of Groningen, Medical Center Leeuwarden), Canada (University of Toronto) and Norway (University of Bergen and Haukeland University Hospital). During 2019, the project has recruited personnel and started experimental and computational work. The kick-off meeting was in September in Bergen.



EV-LiquidBiopsy

- Extracellular vesicles as liquid biopsies for disease

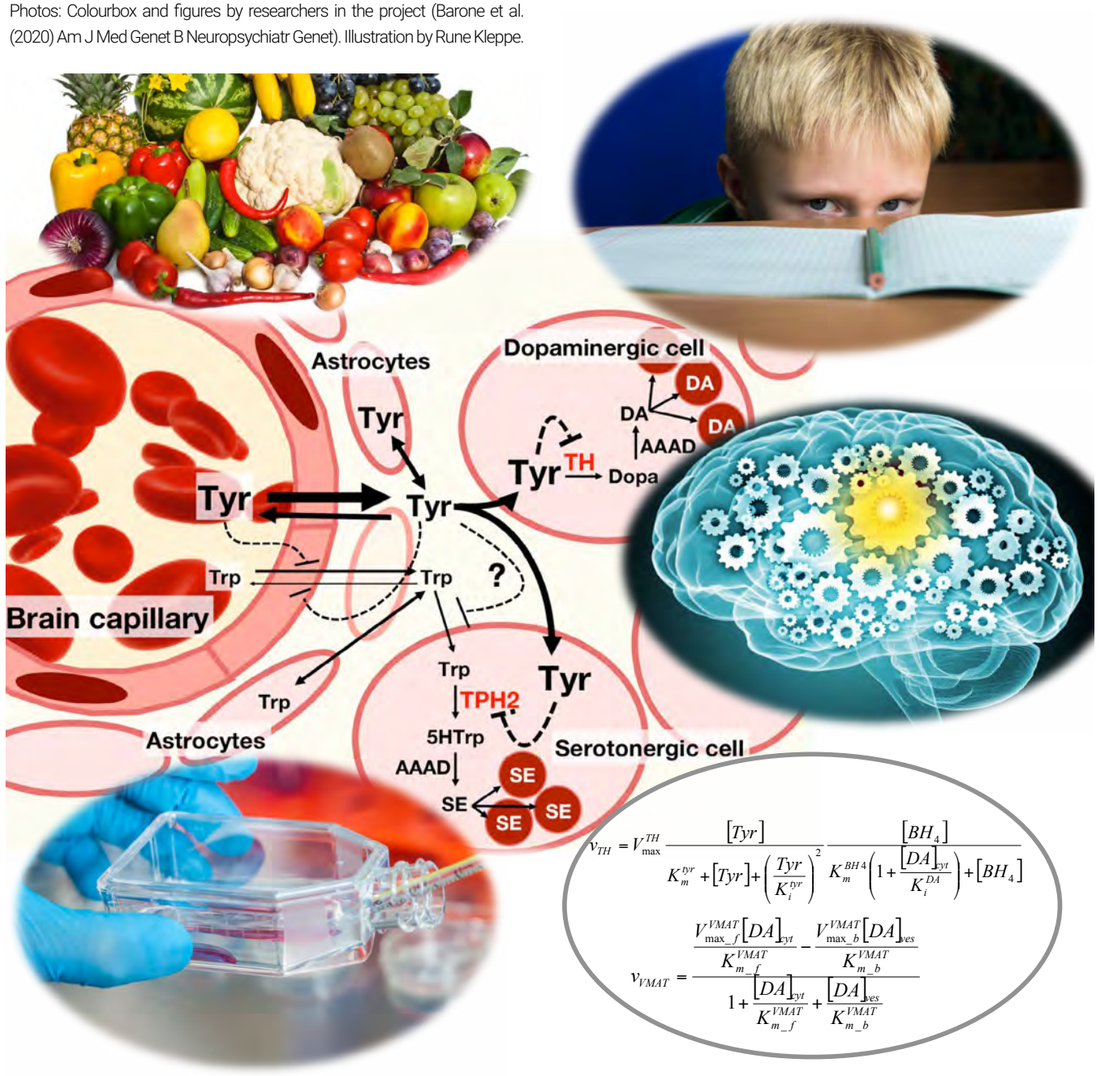
PROJECT LEADER: ALICIA LLORENTE **INSTITUTION:** OSLO UNIVERSITY HOSPITAL

The goal of the project is to develop noninvasive methods for cancer diagnostics based on a new type of liquid biopsies called extracellular vesicles. This year we became a Digital Life Norway partner project and investigated whether the miRNA content of extracellular vesicles found in urine could be used to differentiate different stages of prostate cancer. We have identified several miRNA related to the aggressiveness of prostate cancer by next-generation sequencing. A new set of experiments to validate these findings is ongoing.

In this project, collaboration between biologists, medical doctors, geneticists, analytical scientists, biostatisticians, and bioinformaticians is essential. During the last year we got great input from our international and national collaborators. Our project benefits prostate cancer patients by providing better tools necessary to identify patients that need aggressive treatment. Scientists interested in non-invasive biomarkers will also benefit.

Extracellular vesicles (EVs) are a new type of liquid biopsies. EVs are secreted from cells by direct budding from the plasma membrane (PM) and by fusion of multivesicular bodies (MVBs) with the plasma membrane. EVs contain molecules that reflect the status of the donor cells and can be detected in biofluids. N: nucleus.

Photos: Colourbox and figures by researchers in the project (Barone et al. (2020) Am J Med Genet B Neuropsychiatr Genet). Illustration by Rune Kleppe.



$$v_{TH} = V_{\max}^{TH} \frac{[Tyr]}{K_m^{tyr} + [Tyr] + \left(\frac{Tyr}{K_i^{tyr}}\right)^2} \frac{[BH_4]}{K_m^{BH4}\left(1 + \frac{[DA]_{cyt}}{K_i^{DA}}\right) + [BH_4]}$$

$$v_{VMAT} = \frac{\frac{V_{\max\_f}^{VMAT}[DA]_{cyt}}{K_{m\_f}^{VMAT}} - \frac{V_{\max\_b}^{VMAT}[DA]_{ves}}{K_{m\_b}^{VMAT}}}{1 + \frac{[DA]_{cyt}}{K_{m\_f}^{VMAT}} + \frac{[DA]_{ves}}{K_{m\_b}^{VMAT}}}$$

MEDIATE

- Improved monitoring and treatment of neurometabolic disorders

PROJECT LEADER: JAN HAAVIK **INSTITUTION:** HAUKELAND UNIVERSITY HOSPITAL

The brain relies on a sufficient supply of nutrients and precursor metabolites to maintain its function and development. This is often compromised in metabolic diseases, leading to diverse cognitive disabilities. Inherited metabolic disorders are caused by genetic mutations that severely affect enzymatic functions in one or several metabolic pathways. In this project we focus on disorders of the aromatic amino acid metabolism and how they affect homeostasis of the brain monoamine systems such as catecholamines and serotonin, which are important neurotransmitters and implicated in many neuropsychiatric disorders.

Disorders of phenylalanine and tyrosine metabolism, such as phenylketonuria (PKU), hereditary tyrosinemia type 1 (HT1), and tyrosine hydroxylase deficiency (THD) give rise to aberrancies in the neurotransmission of these transmitter systems. Cognitive comorbidities are therefore common.

The project started in 2019 and involves an interdisciplinary team of researchers, within neuropsychology, medical genetics, cell biology, biochemistry, and mathematical modelling to improve our understanding of how to better monitor and treat these diseases. Within DLN the project can hopefully further develop its transdisciplinary approach where different disciplines are integrated for a better understanding of each other's fields and improving stakeholder involvement.

During 2019 we have hired personnel for the project and published a study on ADHD-like symptoms in Norwegian HT1 patients. We also published a detailed biochemical study on regulation of an important neurotransmitter synthesising enzyme and effects of disease associated mutations.

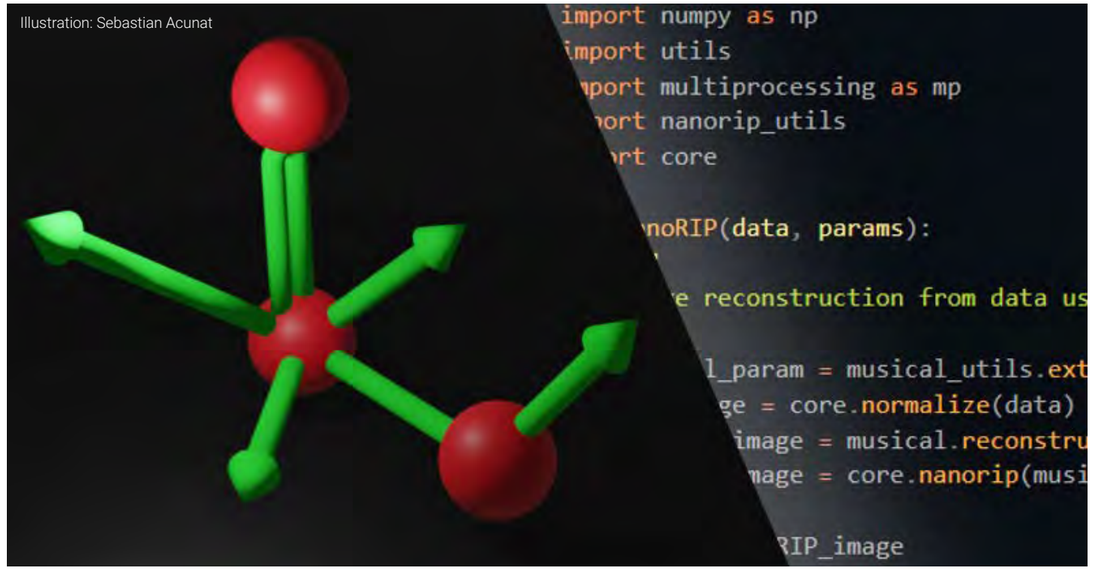


Illustration: Sebastian Acunat

nanoRIP

PROJECT LEADER: KRISHNA AGARWAL **INSTITUTION:** UNIVERSITY OF TROMSØ

nanoRIP is a developing a novel technique for nanoscopy that will provide an isotropic resolution of 80 nm by exploiting the scattering of light between organelles inside the cellular structure. Through innovative symbiotic design of instrumentation and computational algorithms, this information is used to estimate the 3D refractive index of the sample, setting a new paradigm in nanoscopy.

nanoRIP will allow researchers to study life critical processes and events in living cells in natural conditions at nanometer scale by imaging them in non-invasive, minimally photo-toxic, and chemical-free manner. The resolutions are appropriate to observe interactions between sub-cellular components of the cells and with vesicles playing critical roles in triggering events such as healing and death.

The project started in October 2019 and a cutting edge optics lab is currently being set up for the project.

Photo: David Gonzalez/Buendia Photography

The Network Project in 2019

Having presented the research that was conducted in the Centre during 2019, the annual report now documents the accomplishments of the Centre's competence unit that is tasked with advancing the Centre's 'convergence for responsible innovation' mission. The competence unit spans three closely related project grants from The Research Council of Norway.

Firstly, there is the network project, which consists of five work groups: 1) governance & responsible research and innovation; 2) innovation and industry involvement; 3) training and recruitment; 4) competence and infrastructure network; and 5) communication. Secondly, there is the Digital Life research school that is closely connected to the network project's work group 3. Finally, "A road map for academic research-intensive innovation from the Centre of Digital Life Norway" is a new project started in late 2019 that is affiliated with work group 2. These three grants are spread across NTNU, UiO and UiB. The competence unit is led by six professors and sports an interdisciplinary staff of experts in practice – the coordinators.

Two members of the walkshop leaderteam: Maria B. Hesjedal (left) and Liv Falkenberg (right). Photo: Daniël Roelfs

Learning together

If you ask ten people what the Centre for Digital Life is about, expect to receive five or six different answers. Heidrun Åm, leader of DLN Res Publica, argued in her DLN annual conference keynote speech that multiple legitimate conceptions of who values science and how they value it exist in parallel. Digital Life's mission statement, "to create economic, societal, and environmental value for Norway," succinctly illustrates that not all assumptions underlying these conceptions are mutually compatible.

The Digital Life Norway community is having more and more conversations about the expectations and values embedded in research cultures and practices. These conversations are reflection-on-action (Donald Schön), i.e. the kind of reflection we do outside the rhythm of everyday work life. They help us to examine reflection-in-action, the often-informal decisions taken in real-time.

The concept of reflection-on-action was pushed furthest during September's four day "walkshop" where 17 people hiked through rugged terrain outside of cell reception in Jotunheimen. Participants explored the concept of value creation – the elusive yet alluring policy mandate of the Centre[1] . Each evening, a fire-side presentation provided food for thought and discussion during the next day's hike. The radical otherness of the walkshop concept left a positive impression beyond the participants themselves, as stories about the experience begin to circulate in the Centre at large (cf. p.72 research school contribution to annual report).

In 2019 the workgroup on responsible research and innovation (RRI) enabled such reflection-on-action in a number of ways. In April, staff from most of the DLN research projects gathered at a workshop to share their practical experiences with RRI. Also during Spring, the DLN governance group that includes RRI worked with the Research Council of Norway to prepare the midterm self-assessment of the Centre. This Lysaker egenvurdering gathered some 30 participants (coordinators, senior and junior researchers, board members, Research Council officers and invited experts). The participants assessed the current state of the Centre and made concrete plans for the way forward. The key conclusions of that meeting were:

- Fostering cross-disciplinary collaborations in biotechnology research with a focus on modeling remains a highly relevant topic
- The Centre cannot accomplish these collaborations without the support of a strong vision
- What the Centre has accomplished to date is a steppingstone on the way to more ambitious goals

The self-assessment process was built on the achievements of the 2018 Selbu search conference (cf. annual report 2018). That conference has proven to be an invaluable planning resource for the Centre's coordinator team. It has also given the Research Council confidence that DLN can self-critically and productively assess its own progress and future direction

What are the lessons from four years of RRI work in DLN? We suggest:

- "Projects" are a somewhat arbitrary subset of what researchers do and are described in terms of promised performance outcomes. This is also true of RRI. The researchers' ability to write project proposals rarely predict their ability to engage with societal responsibility.
- Several research projects address similar societal issues. Dedicated and experienced staff is required to identify such issues, to provide initial momentum to start collaborations between the research groups concerned, and to introduce complementary expertise from the social sciences and humanities.
- Unpacking and discussing the complexities of DLN's research policy requires nurturing of a sense of community. Professionally managed strategy seminars and engaging of junior researchers is particularly important.

Participants of the RRI workshop in April. Photo: Hilde Zwaig Kolstad

1 https://digitallifenorway.org/gb/blog/four-days-50km-and-a-question-what-is-of-value

Reinold Ellingsen (left) and Sven M. Carlsen (right) have learned a lot about innovation through collaborating with Alexandra Patriksson. In the latest meeting they presented exciting findings from their research, which runs parallel to the innovation work. – Alexandra is a useful and obliging team player. And we can even share research problems with her, and she in fact understands what we are working on, they say, while referring to Patriksson's background as a bio engineer, in addition to her knowledge of innovation. Photo: Hilde Zwaig Kolstad

Cultivating an innovation mindset from day one

As the fourth year of the Centre for Digital Life Norway's (DLN) operation comes to a close, it is time to reflect on how our associated research projects have benefitted from the innovation support, individual counseling, and education that DLN provides. We coordinated meetings that led to exciting new collaborations, guided researchers through the jungle of grants to fund activities needed for the innovation work, and helped them navigate the difficult, expensive and time consuming process of developing socially beneficial innovations from their academic research. Below are stories that highlight DLN's dedication to helping research projects achieve their innovation potential.

A VALUABLE EXCURSION TO UPPSALA

Dirk Linke is a microbiologist at the University of Oslo (UiO) and the Principal Investigator of the DLN research project BEDPAN. The project develops a way to produce palladium nanoparticles using bacteria. On a rainy morning in May, he and three others — PhD candidate Nadeem Joudeh, DLN Innovation Advisor Alexandra Patriksson, and Collaboration Manager, Lise Rødsten, from the technology transfer office Inven2 — made their way to the oldest university in the Nordic region to learn about potential areas of application for his nanoparticles of interest to industrial businesses.

The main objective of DLN is to create societal value from biotechnological research and innovation through transdisciplinary collaborations. Linke and his colleagues knew they had made an exciting discovery, but as microbiologists they weren't sure what the commercial applications were. During the day at Uppsala, the four met with experts in the fields of material sciences, chemistry, and innovation who offered new insights into uses for BEDPAN's nanoparticles. The meeting was so successful that Linke and one of the Uppsala researchers agreed to initiate collaboration and apply for funding from the European Union together. Linke credits the innovation support he received through DLN for making this possible.

In addition, Lise Rødsten at Inven2, used what she learned from this trip to continue to look for possible markets for Linke's nanoparticles. She is currently contacting companies to initiate collaboration and development. Thanks to funding and consulting from DLN, she was able to get involved with the BEDPAN project at an early stage, rather than having to wait until they progressed further in their innovation process.

DLN Innovation Advisor Alexandra Patriksson is responsible for offering support, like this trip to Uppsala, to the research projects of the Centre. She acts as a mediator of ideas and facilitates the innovation work by helping the researchers identify what needs to be done and when, and to find partners and funding to execute the plans. Patriksson is conscious of DLN's role in innovation development.

Sven M. Carlsen, Project Leader of the DIAP project, has had great use of the innovation support he has received through DLN. Photo: Hilde Zwaig Kolstad

STEPPING IN WHERE TTOS HAVE TO SIT BACK

Sven M. Carlsen and Reinold Ellingsen of the DLN project Double Intraperitoneal Artificial Pancreas (DIAP) at the Norwegian University of Science and Technology (NTNU), are developing an artificial pancreas to regulate glucose levels in patients with diabetes type 1.The idea has significant commercial potential for a large patient group but because their project is still at an early stage, there are many questions yet unsolved when it comes to the commercial path. The university's TTO helps the project keep control of the Intellectual Property (IP) landscape but has limited capacity to develop the commercial strategy and plan at this stage.

Thus DLN brought in its own dedicated innovation support and assisted in giving the project a initial overview of the commercial market for their product and bringing the relevant questions to the local TTO's attention. They, in turn, have made thorough investigations of the patenting landscape. Much to the dismay of the project, the TTO has discovered that their market is flooded with existing patenting, making it difficult to find a niche for their product.

Fortunately, the project was granted milestone funding from the Research Council of Norway (RCN) after having received crucial support from DLN and the TTO during the application process. These funds will allow DIAP to hire external experts to survey their research and provide a patent strategy. Both Carlsen and Ellingsen emphasize the milestone application was only possible because of the advice and motivation that DLN gave them and their TTO.

THE ART OF RIDING TWO HORSES AT THE SAME TIME

Researchers face a conflict between the drive to publish in public journals and the need to hold back their scientific findings in order to secure patents and develop innovation. «It is problematic that you have to be cautious about sharing information when something could potentially be patented» says Astrid Aksnes, the project leader

for the DLN project Lab-on-a-Chip at NTNU. Together with Alexandra Patriksson, she attended the Innovation Management course offered to the DLN project managers by the RCN each year. A part of the programme was a week in Silicon Valley where they got direct feedback on the business plan of the project from local innovation experts.

Several of the researchers in the DLN share the concern about the conflict between necessarily protecting ideas for innovation purposes and publishing findings. They emphasize the benefit of having DLN support their commercialization efforts. Linke says that both he and his colleague in the BEDPAN-project, Nadeem Joudeh, must often remind themselves that they need to balance their time between the innovation required by RCN grants and doing their research. «There is a real conflict between research work and innovation development. It takes tremendous time and expertise to develop innovation from a research idea -both in short supply with researchers who are experts in their research fields, but do not necessarily know about developing products and services for market».

Sven M. Carlsen from the DIAP project believes that the support that they have received from DLN is very helpful and much-needed to combat this conflict: «Let those who are good at it do what they are good at», he states, referring to Patriksson.

LOOKING FORWARD

Researchers who have worked on innovation development with the support of DLN say they have learned a lot. From understanding the commercialization process and finding the right collaborators, to training and grant writing assistance, DLN has made invaluable contributions to their work. Looking forward, DLN plans to increase the capacity to support researchers through innovation-oriented activities. It will continue to work with researchers and their TTOs to help with research and business development. «The Centre for Digital Life has found a place in the innovation ecosystem where we can make a difference, and we will continue to explore and develop this», predicts Alexandra Patriksson.

One of the five meetings that Astrid Aksnes and Alexandra Patriksson participated at together, through the course in innovation management and commercialisation, took place in Silicon Valley. Among others, they were instructed at Faculty Club at Stanford, by Justin Ferrell from dSchool. Patriksson is number two from right. Photo: Private.

Photo: Hilde Zwaig Kolstad

The Digital Life Norway Research School

The research school incorporates the ideas behind The Centre for Digital Life into training and meetings for early career researchers. Through events such as the annual conference and walking workshops, a majority of the Research School's 300+ members are now associated with Digital Life and the network surrounding The Centre. The Research School is stimulating a transdisciplinary way of thinking and working to create favourable conditions for the new biotechnology field.

A PLACE TO MEET

The annual conference is the research school's premiere event where early career researchers can meet new friends and collaborators. Around 80 members participated in the 2019 conference in Bekkjarvik, outside Bergen. The conference featured CV-building workshops and career advice, an innovation workshop where participants could develop their own projects, and a special focus on stress management and mental health. This year, participants sent in and exchanged short

bios before the conference to facilitate networking and socializing. The 2019 organizing committee consisted of PhD students Marte Jenssen (UiT), Eric Juskewitz (UiT), and Shahin Sarowar (UiB), and postdocs Zeeshan Muhammad (UiB) and Kanhaiya Kumar (NTNU).

STUDENTS TEACHING STUDENTS

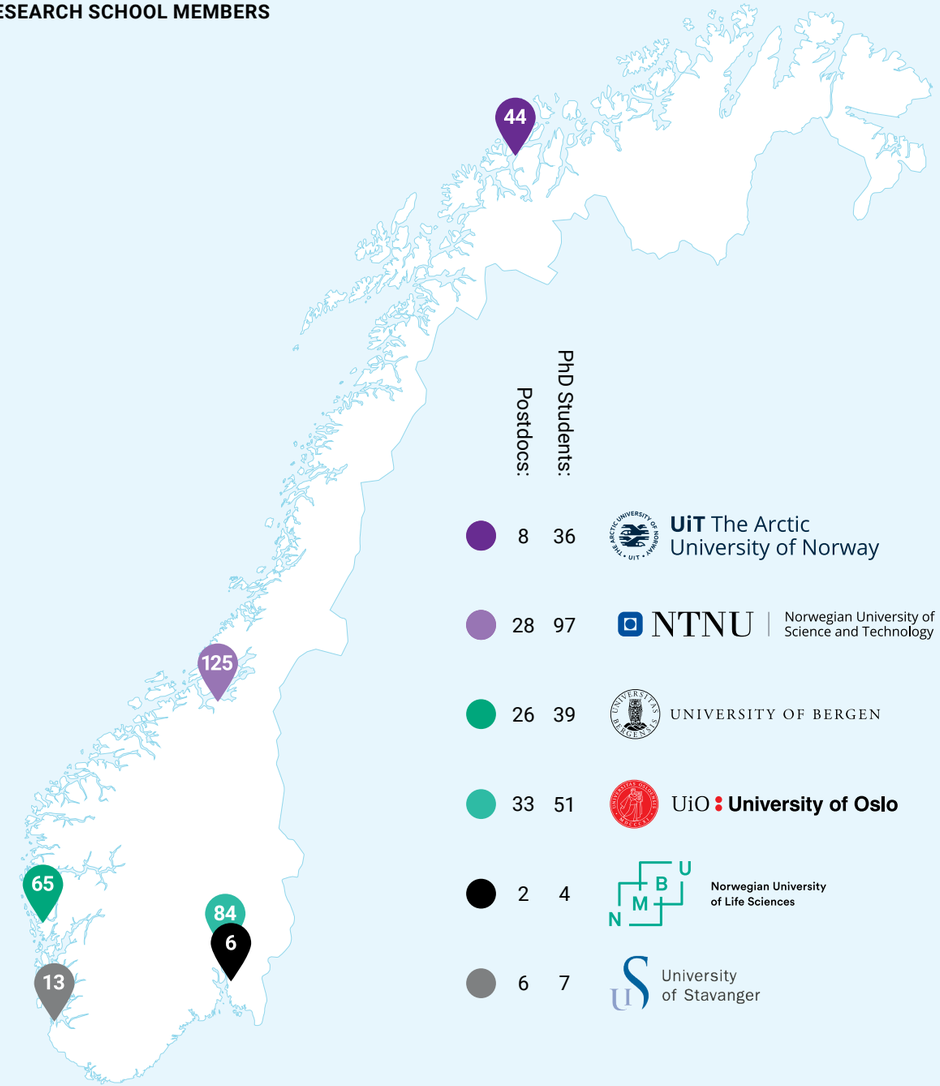
Two of the 24 courses and events offered by the research school in 2019 were initiated and organized by research school members. PhD students Christian Schulz and Lisa Tietze managed to get NTNU's entire department of design on board for an illustration course for researchers in life sciences. The course, "Pic' Up Your Game," had an overwhelmingly positive response with almost 60 applications to participate. It clearly filled a need for PhD students and postdocs who are facing increasing pressure to present their research in new and accessible ways. The research school will continue this collaboration, and organize a similar course in 2020.

At the University of Bergen, a group of postdocs organized a 'Sandwich Course', introducing the participants to the interplay of different research fields in drug discovery. This course gave the participants a brief insight into neighbouring disciplines, making it easier for them to initiate transdisciplinary collaborations. Big thanks to UiB's Åsmund Kaupang, Fahimeh Khorsand, Zeeshan Muhammad, and Christoph Bauer.

GOING TO THE MOUNTAIN

The aim of Digital Life Norway is to "create economic, societal, and environmental value," but what is of value and how do we value it, and how can the biotechnology of the future create and sustain value? These were the discussion topics on a recent "walkshop," organized by The Centre's working group for RRI and the research school, in beautiful Jotunheimen. Over 5 days, an equal number of men and women —professors, PhD candidates, postdocs, and others — from eight nations spent time pondering these questions. Conversations flowed easily and they listened to the opinions of the people around them while walking in the vast landscape. Plenary moments for reflections in front of the cabin fireplace each evening nicely wrapped up the discussions that had taken place during the day. A special thanks to Maria Hesjedal, the NTNU PhD student with extraordinary hiking and herding skills.

THE RESEARCH SCHOOL MEMBERS



Stimulating synergies and transdisciplinarity across projects

A key feature of the research in DLN is bringing together perspectives from different disciplines to develop new perspectives and competencies. Below are some examples of organized meetings and collaboration between projects that make this happen.

APPLYING CONTROL ENGINEERING TO BIOLOGICAL PROCESSES

For many years, control engineers have developed methods to analyse complex networks of regulatory interactions. These methods may help researchers to understand the underlying regulatory mechanisms in living organisms. A recent workshop at the University of Stavanger focused on how to apply these methods to homeostatic mechanisms and control loops that are key to robust physiological processes. Researchers within The Centre met with control engineers at UiS, and international researchers to discuss how these methods can be applied to better understand biology and improve models of living systems.

LECTURE AND SEMINAR SERIES VOLTERRA LECTURES

The Volterra lectures are a series of high profile talks given by internationally renowned scientists at DLN-associated institutions. All invited lecturers are recommended by DLN researchers. This year, we saw presentations form Christopher Voigt, Professor at MIT and Omid Farokzhad, Professor at Harvard Medical School. These lectures are a great opportunity for our researchers to learn new skills and develop collaborations.

The Voigt lab is well known for their contributions to synthetic biology. In his Volterra Lectures at UiO, NTNU, and UiB, Professor Voigt showed us how they program cells using designed synthetic genetic circuits that enable bacteria to perform highly complex computations.

Professor Farokzhad's Volterra Lecture described how to translate biomedical research into products and cures. As director of The Center for Nanomedicine at Brigham and Women's Hospital, he has been involved in developing a myriad of nanotechnologies for medical applications and founded several biotech companies.

Chris Voigt's Volterra lecture in Bergen. Photo: Rune Kleppe.

DIGITAL BREAKFAST

Digital Breakfast is a DLN seminar series that combines a real breakfast with scientific talks showcasing interdisciplinary work involving computational or mathematical approaches to biosystems. The talks cover a wide range of themes and occasionally collaborate with other initiatives like the Norwegian Biochemical Society. We are happy to announce that during 2020 we will also be collaborating with NORA, the Norwegian Research network, on AI.

SYNERGIES IN THE DIGITAL LIFE CONSORTIUM THROUGH PROJECT COLLABORATIONS

The Centre offers funding to support collaboration between research projects associated with DLN under the "Cross-project Activity" calls. During 2019, several collaboration efforts took place as a result of this funding.

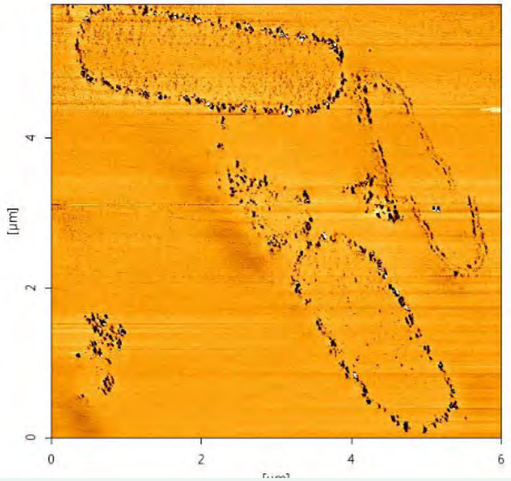
Atomic force microscopy to monitor bacterial palladium nanoparticles.

A project that enabled researchers to visualize the magnetism of bacteria-produced palladium nanoparticles was the result of a collaboration between the BEDPAN project, which engineers palladium nanoparticle-producing bacteria and the BioZEment 2.0 project, which uses technology that can monitor this process

Methods for lipidomics.

In the AurOmega and DigiSal projects, the Bruheim lab at NTNU is developing many methods for characterising metabolites and lipid molecular species in biological samples. This caught the interest of researchers in the dCod 1.0 project, as many pollutants change the regulation of genes involved in lipid synthesis and turnover. Enabled the labs to perform initial analysis of the cod liver lipidome.

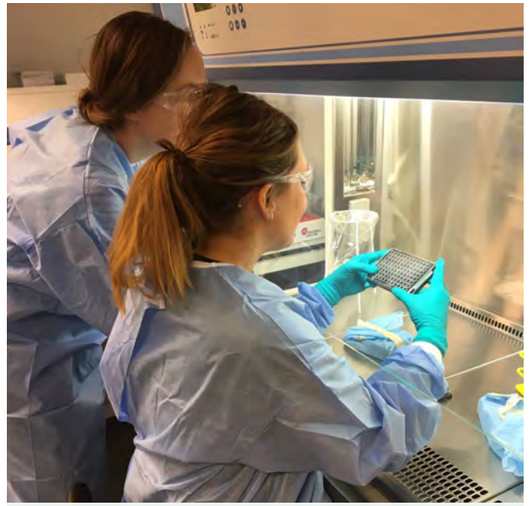
Cod liver harvesting. Photo: Karina Dale, dCod 1.0 project.



Large cluster of magnetic nanoparticles on the surface and inside bacteria. Photo: Pavlo Mikheenko, BEDPAN project.

Genome scale metabolic reconstruction workshop.

In April 2019, dCod 1.0 and DigiSal co-organized a workshop on genome-scale metabolic model reconstruction. Steinboligen at Finse (http://steinboligen.no) was chosen as the venue and served as a beautiful backdrop for interesting discussions, hands-on sessions, and socialization. In total, 12 participants from Digital Life associated projects, including dCod 1.0, DigiSal, and modellers from Almaas's group working in the INBioPharm, BioZEment and AurOmega projects joined the workshop. In addition, two guest experts in the RAVEN 2.0 toolbox for metabolic reconstruction were invited from the Chalmers University of Technology in Gothenburg, Sweden. Check out the video from Maksim Zakhartsev to get a better impression of beautiful Finse:



Co-culturing of leukaemia- and stroma cells in 3D. Photo: Hanne Haslene-Hox, 3DLife project

Analysis and management of complex biological data.
Biological data sets often have high dimensionality and heterogeneity. This makes it challenging to extract statistically valid biological knowledge. Methods that can cope with these challenges are equally important for data analysis in cancer as in cod toxicology. Through collaborations and workshop meetings, mathematicians and bioinformaticians from the dCod 1.0 project successfully applied their methods to the high dimensionality data from researchers in the DLN partner centre The Centre for Cancer Biomarkers (CCBIO). At the workshops, researchers also addressed challenges and shared their experiences managing and analysing such data sets.

Testing chip technology on biomarkers for environmental pollutants.
Lab-on-a-Chip and dCod 1.0 collaborated to investigate the application of a new detection technology using dCod 1.0 biomarkers. Surfaces developed in the Lab-on-a-Chip project were using monoclonal antibodies for cod vitellogenin, a fish plasma biomarker for endocrine disrupting reagents, supplied by Biosense Laboratories AS. Using this set-up, researchers performed experiments to quantify the presence of biomarkers in fish samples. When optimized, this chip technology can be used to simplify and speed up environmental monitoring.

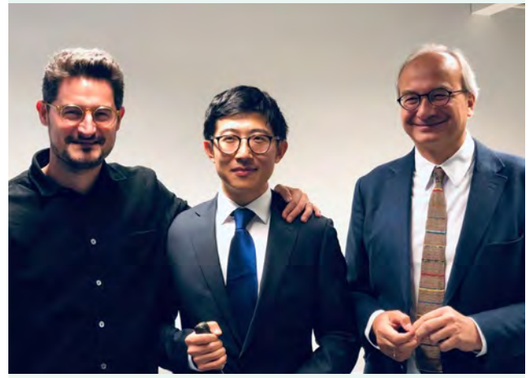
3D leukaemia cell co-culture.
During 2019, the 3DLife project in Trondheim and a research group from CCBIO in Bergen initiated a collaboration project. They aimto explore heterotypic cell interactions and sensitivity towards tyrosine kinase inhibitors in Acute Myeloid Leukaemia (AML). The researchers established a co-culture 3D structure using alginate gels to mimic the leukemic bone-marrow microenvironment. The co-culture setup was achieved by encapsulating the two cell lines in different ratios in the 0.5% alginate gel. Researchers were then able to test the different cell environments for differences in drug sensitivity.

PRIZE FOR TRANSDISCIPLINARY PUBLICATION 2019

The award is given to research projects in the Centre that have published studies resulting from highly interdisciplinary research efforts. In addition, to stimulate visibility of the DLN research, there is a strict criterium for Digital Life funded projects, that the awarded publication(s) clearly states its association to the Centre for Digital Life Norway.

The 2019 prize for "Transdisciplinary publication of the year" was awarded to the partner project PerCaThe, for the paper "Toward Personalized Computer Simulation of Breast Cancer Treatment: A Multiscale Pharmacokinetic and Pharmacodynamic Model Informed by Multitype Patient Data", published in Cancer Research. The publication is an excellent example of how computation and modeling can be applied to clinical data and move translational research closer to clinical applications.

Authors of the awarded article looking to histological samples from patients together, mathematicians, pathologists and oncologists side by side. Photo: Xiaoran Lai.



The thesis defence of Xiaoran Lai (middle), with the two supervisors and last authors of the paper, Arnoldo Frigessi (right) and Alvaro Köhn-Luque (left). Photo: Oslo Centre for Biostatistics and Epidemiology, UiO.

Advancing sustainable research data management

The Centre for Digital Life is committed to sustainable data management practices and improving data management infrastructure. In 2019, we worked with partners tow develop new infrastructure and hired new staff to assist our affiliated researchers. DLN is leading the adoption of findable, accessible, interoperable and reusable (FAIR) data management in the Norwegian Life Science landscape and we are excited to see an increasing number of institutions that include FAIR principles in their policies. Looking forward, we will continue to develop best practices for data management and encourage collaboration with organizations outside of DLN.

In 2019 we partnered with ELIXIR Norway to develop several projects to improve data management infrastructure for our affiliated researchers. Together with ELIXIR Norway, we are providing access to the Data Steward Wizard: an interactive questionnaire to generate data management plans that follow the criteria from funding bodies within Science Europe, including the Norwegian Research Council. Some of our research projects, including dCod 1.0, have already started to use the new integration of the open source SEEK platform from FAIRDOM with another ELIXIR Norway solution, NeLS (Norwegian e-infrastructure for Life Sciences). Thanks to this partnership, we were able to recruit a highly competent coordinator for data management, Korbinian Bösl, who started late 2019. He works with both DLN and ELIXIR to improve data management for researchers across Norway.

We were also able to identify a partnership to further improve infrastructure in the future: BioMedData, a consortium led by ELIXIR Norway, is a natural fit for us. Its aim is to make data management easier for researchers by improving the way research infrastructures provide data and metadata to their users.

Many of our infrastructure improvements have been inspired by interactions with our affiliated groups. Together with the DLN Research School and the Norwegian Research School in Neuroscience (NRSN), we organized a three-day workshop "Data Management for Neuro and Life Scientists". We gathered noted experts in the standardisation of data formats and analysis workflows for neuroscience data and covered both basic and advanced data management within existing management platforms. The workshop included a new versatile data format called Exdir , developed by one of our research projects DigiBrain, and leading international initiatives, such as Neurodata Without Boarders and DataJoint.. The second part covered both basic and advanced data management within the SEEK and NeLS platforms and the usage of reproducible bioinformatics pipelines implemented in Galaxy. We were very happy that the leading developers of SEEK from the FAIRDOMHub community provided training on their application programming interfaces.

NORWEGIAN METABOLOMICS NETWORK

Technologies for Digital Life is one of our interfaces towards infrastructures. In 2019 we invited to a network meeting within metabolomics, a field of fast-growing interest and importance for DLN. The meeting brought together specialist groups and core facilities from institutions across Norway, experts with demanding modelling requirements, and existing national infrastructures with technologies applicable to metabolomics. During the meeting it became clear that there was a need for a national network within the field. There are now ongoing efforts to kick-start such a network to build the necessary competences for establishing technologies and applications. This could lead to more synchronized and collaborative development of technologies for metabolomics in Norway.

End-to-End Data management toolkit for Life Scientist in Norway: Together with ELIXIR-Norway and FAIRdom, Digital Life Norway has assembled and financed a solution that covers the whole data life cycle and provides infrastructure components from concept to publication.

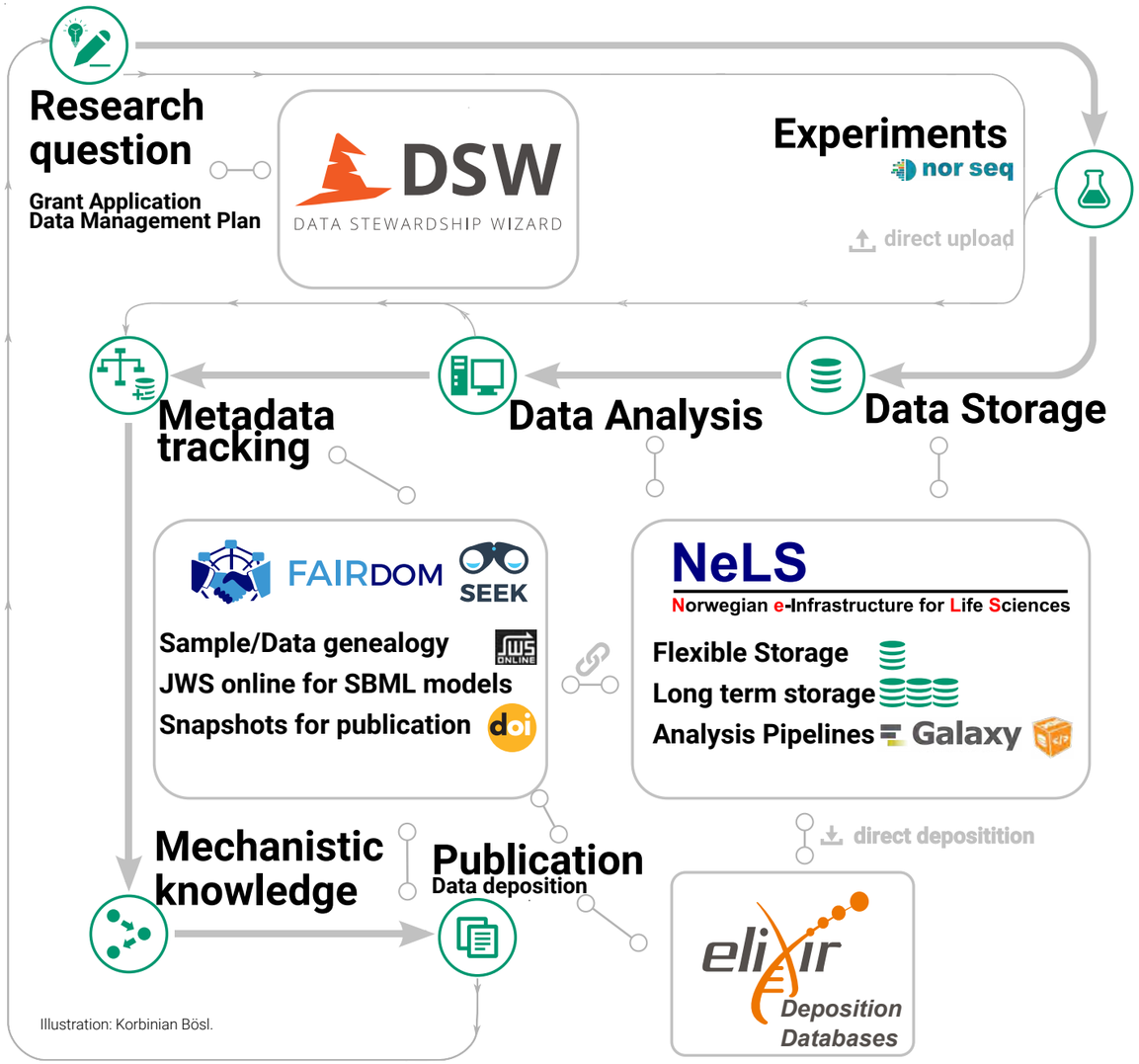


Illustration: Korbinian Bösl.

Arnoldo Frigessi, Project Leader of BigInsight and PerCaThe projects, at Arendalsuka, presenting some of his and his colleagues' research on the use of artificial intelligence in developing personalized cancer treatment. Photo: Hilde Zwaig Kolstad.

Fostering an engaging Digital Life community

The Centre for Digital Life Norway (DLN) engaged with the general public, civic leaders, the greater research community, and research institutions during several communication events this year. These highly productive conversations led to a better understanding of DLN and our member projects' activities and helped us develop new ways for us to provide value to the public.

REACHING PROFESSIONALS AND POLITICIANS WITH THE LATEST RESEARCH

One of the highlights of this year was Arendalsuka, the annual festival for civic leaders and people who are interested in public policy. Policy makers, researchers, interested members of the public, and journalists packed into the former mess hall at the M/S Sunnhordland to hear from, amongst others, two Digital Life Norway community researchers talk about the immediate health challenges we face as part of the event «Technology for better health: Innovation and citizen management».

Arnoldo Frigessi, project manager of the BigInsight and PINpOINT research projects, shared his expertise on the use of digital methods and artificial intelligence to develop personalized cancer treatments. Meanwhile, John-Sigurd Mjøen Svendsen, project manager of the DigiBiotics research project, explained how he and his colleagues at the University of Tromsø are using machine learning to find new antibiotics based on less common molecules found in the Arctic Sea.

Svendsen also represented DLN in a subsequent panel discussion about the challenges of transforming basic research into applied health technology, an event co-organized by the University of Oslo and The Centre. Both Frigessi's and Svendsen's messages at Arendalsuka were further taken up in an article in the scientific periodical «Norsk Farmaceutisk Tidsskrift», titled: ***Promising the tool that will provide future antibiotics – DigiBiotics combines marine biology and digital technology to save the world from antibiotic resistance***, which reached pharmacists all across the country.

Another representative of DLN at Arendalsuka was the Centre Leader, Trygve Brautaset. In a debate about how gene-modified food should be regulated, hosted in a collaboration with the Norwegian Biotechnology Advisory Board, he stressed the importance of researchers building trust over their work.

PRESENTING THE CENTRE FOR DIGITAL LIFE NORWAY AT NORDIC LIFE SCIENCE DAYS

Nordic Life Science Days in Malmö was another great outreach experience in 2019. The three-day conference and networking event gave us a valuable opportunity to share relevant research with potential collaborators and investors. We brought brand new one-page leaflets that directly and clearly explained the different aspects of four DLN life science research projects. The one-pagers made these research projects easier to promote and was a welcome networking hand-out.

THE CENTRE'S INFORMATION CHANNELS

DLN's primary goal is to encourage responsible convergence and collaboration for innovation within in the digital biotech research field. To accomplish this goal it is essential that we facilitate dynamic communication between The Centre's various researchers so they can share their competencies. In 2019, we accomplished this communication with a monthly newsletter and regular, strategic use of social media channels. As a result of these efforts, the Centre's participants could find out about relevant work in other projects and share their own research with others.

These established channels of communication are also an effective means for the researchers to receive information about the RRI, data management, innovation, training resources, and support that The Centre has to offer. In late December, we posted a long-read article on our web site that explained some of the specific innovation work being done in DLN. We used the newsletter and social media channels to bring the article to the attention of our audience of DNL researchers.

BRIDGING COMPETENCES: DIGITAL LIFE CONFERENCE 2019 & GUEST LECTURES

The Centre's communication efforts run in harmony with all of its activities. Still, the 2019 Annual Conference and the Volterra Guest Lecture Series held special value for communication.

The annual conference, Digital Life 2019, took place in Tromsø in September of this year. Around 80 senior and early-career researchers from the DLN community gathered for two days of knowledge sharing, good discussions, and networking. Nearly 50 posters and four plenary presentations by DLN-researchers sparked engagement. The program included five international keynote lectures on: antimicrobial research, value creation and the public good in research, digital twins in health research, ambitions to sequence the genomes of all eukaryotic life on earth, use of systems biology approaches for personalized medicine, and research-based innovation in biotechnology.

The four Volterra guest lectures in 2019 (cf. p.74) were our other communication event highlights. An acclaimed American researcher, Christopher Voigt, was invited to Oslo, Trondheim, and Bergen to give his perspectives on cell programming, and another, Omid Farokzhad, to Bergen to present ways to translate biomedical research into products and cures.

Over 80 researchers gathered in Tromsø for the annual conference of the Centre for Digital Life Norway in September. A varied scientific program, around 50 posters and plenary presentations sparked many engaged discussions and helped establish new connections. Photos: David Gonzalez/ Buendia Photography.

People

From the 'Walkshop', hosted by the Centre for Digital Life Norway in mighty Jotunheimen, September 2019. Photo: Daniel Roëlfs


Photo: David Gonzalez/Bilendia

The coordinator team

The Network Project coordinator team of 2019, from left: Brage Hansen, administrative support, Liv Eggset Falkenberg, Research school Coordinator, Rune Kleppe, Data Management Coordinator, Marie Hjelmseth Aune, Centre Coordinator, Raffael Himmelsbach, Responsible Research and Innovation and centre Coordinator, Alexandra Patriksson, Innovation Coordinator and Hilde Zwaig Kolstad, Communications

Coordinator.Fatemeh Zamanzad Ghavidel (left) is another Data Management Coordinator and post doc in the DLN Network Project team.

Korbinian Bösl
Data Management coordinator, joined the Network Project team from the University of Bergen in 2019.

Leaders of the Network Project

Arnoldo Frigessi
Professor UiO, leading the Innovation/Industry involvement work group

Inge Jonassen
Professor UiB, leading the Data Management/ Competence and infrastructure work group

Kjetill S. Jakobsen
Professor UiO, leading the Communications/ Inreach and out-reach work group

Olav Haraldseth
Professor NTNU, leading the Research School/ Training and re-cruitment work group

Roger Strand
Professor UiB, leading the Responsible Research and Innovation (RRI) work group

Trygve Brautaset
Professor NTNU and Centre leader

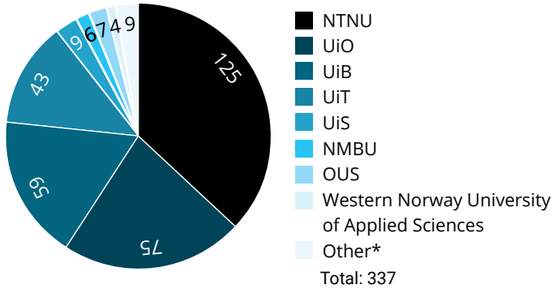
New members of the Digital Life board

Marit Bakke
Vice Dean of the Faculty of Medicine at the University of Bergen

Peder Heyerdahl Utne
Head of the Research Administration at the Oslo University Hospital

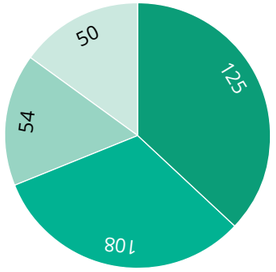
2019 at a glance

DLN RESEARCH SCHOOL MEMBERSHIP BY UNIVERSITY



Total: 337

MEMBERS DIGITAL LIFE NORWAY RESEARCH SCHOOL

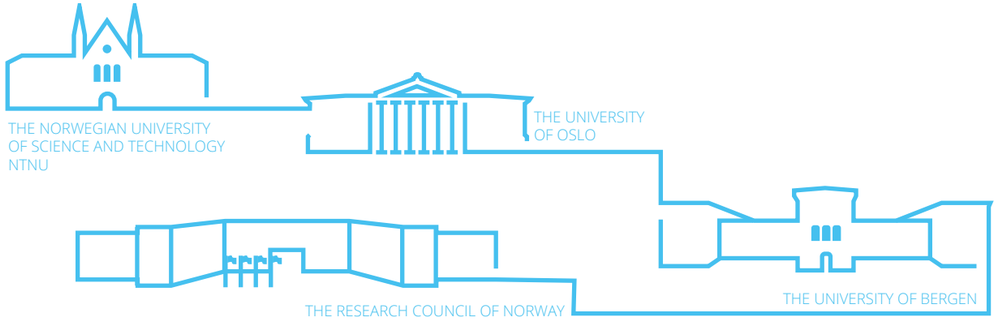


Total: 337

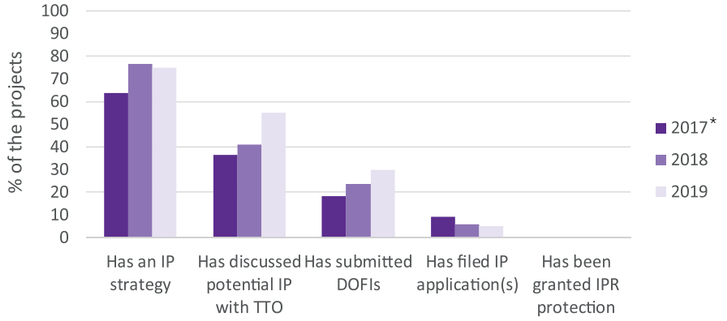
* Other institutions include: Nord University, NORCE, NOFIMA, NIBIO, OsloMet and University of South-Eastern Norway.

44% more members

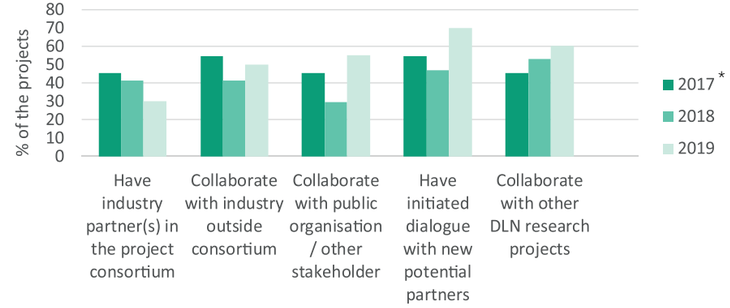
CENTRE FOR DIGITAL LIFE IS FINANCED BY:



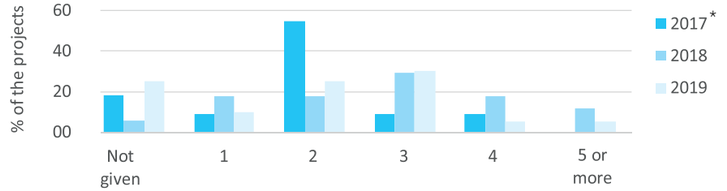
IP AND COMMERCIALIZATION



COLLABORATIONS



NUMBER OF POTENTIAL BUSINESS IDEAS



*Number of DLN projects were 19 in 2017, 24 in 2018 and 36 in 2019

The timeline of the 2019 DLN events

18.-20. February
Scientific Writing Workshop

11.-15. February
Course: Creating Scientific Illustrations

01. February
Digital Frukost - Visual Data Science and the Integration of Interactive and Automatic Data Analysis

28. January
Seminar: Patenting & Publishing - The Whys and Hows

08. March
Digital Frukost: Searching for Solutions to Trade-Offs Among Ecological Mechanics, Behaviour and Physiology

05.-14. March
Workshop: Collaborative Scientific Software Development

29.-30. April
Workshop: Building The Digital Life Norway Community on Responsible Research and Innovation

07.-10. May
Volterra Lectures: Christopher Voigt - Programming Cells

14. May
Volterra Lecture: Omid Farokzhad - Perspectives on How to Translate Biomedical Research to Products And Cures

15.-16. May
Workshop: Towards in Silico-Guided Clinical Trials in Cancer

20.-22. May
Workshop: Control Engineering Concepts in Systems- and Synthetic Biology

04.-06. June
3rd Annual Conference of Digital Life Norway Research School

26. September
Frokostmøte om Billedbehandling – AI og Håndtering av Store Datamengder

26. September
Symposium: Systems Medicine - From Data to Clinical Application

20. September
Digital Frukost - The Circular Economy: Thermodynamic Impossibilities and Public Policy

09.-13. September
Walkshop: Creation of Value

05. — 06. September
Digital Life 2019 Conference

24.-28. June
Workshop: Fish Under Stress - Systems Biology and Mathematical Modeling

17.-21. June
Sandwich Course - Experimental Techniques in Drug Discovery

14. June
Digital Frukost: Computational Medicine in the Age of Digitalisation and Super-Complexity

23.-26. September
Course: «Pic' Up Your Game» - How to Make those Figures Rock Your Science

14.-16. October
Scientific Writing Workshop

22.-25. October
Normic Workshop on Microscopy Image Processing

04.-08. November
Course: Metabolic Pathway Analysis

06.-08. November
Workshop – Getting Your Hands-on Data Management

19. November
Symposium: Technologies For Digital Life - Metabolomics

21. November
Mini-Seminar In Metabolomics

29. November
Digital Frukost: Multidisciplinarity in Environmental Sciences: How to Link Data and Information

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