International Synthetic Biology Workshop

20 – 22 March 2023

The Sense-Compute-Response Paradigm

Organizer: Beatrix Suess & Heinz Koeppl

Speakers

KATE ADAMALA University of Minnesota, USA
GREGORY BATT Institute Pasteur, France
JAMIE DAVIES University of Edinburgh, UK
BARBARA DI VENTURA University Freiburg, Germany
TOBIAS ERB MPI Marburg, Germany
ELISA FRANCO UCLA, USA
PAUL FREEMONT Imperial College London, UK
JÖRG HARTIG University Konstanz, Germany
MUSTAFA KHAMMASH ETH Zürich, Switzerland
SEBASTIAN MAERKL EPFL Lausanne, Switzerland
VITOR MARTINS DOS SANTOS Wageningen University, Netherlands
ANNE MEYER University of Rochester, USA
ANDREAS MÖGLICH University Bayreuth, Germany
HENRIKE NIEDERHOLTMEYER TU Munich, Germany
VINCENT NOIREAUX University of Minnesota, USA
CYNTHIA SHARMA University Würzburg, Germany
OSKAR STAUFER Leibniz INM Saarbrücken, Germany
ROBERT TAMPE University of Frankfurt, Germany
BRITTA TRAPPMANN MPI Münster, Germany
WILFRIED WEBER Leibniz INM Saarbrücken & University Saarland, Germany

FOR MORE INFORMATION VISIT

WWW.TU-DARMSTADT.DE/SYNBIO

20 March 1 pm – 22 March 2 pm S2/08, Hochschulstr. 4, Darmstadt

Centre for Synthetic Biology

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International Synthetic Biology Workshop

Program 20 March 2023

The Sense-Compute-Response Paradigm

13:00 - 13:20	Official Opening
13:20 - 14:05	**TOBIAS ERB** MPI Marburg, Germany Opening Talk
Session I **Cell Free Synthetic Biology**	**Chair: Viktor Stein**
14:05 - 14:40	**VINCENT NOIREAUX** University of Minnesota, USA Prototyping and building biochemical systems using cell-free gene expression
14:40 - 14:55	**DORA TANG** MPI Dresden, Germany Feedback communication in populations of synthetic cells
14:55 - 15:30	**ELISA FRANCO** UCLA, USA Dynamic control of nucleic acid condensates
15:30 - 16:00	Coffee Break
Session II **Genetic Circuits Design**	**Chair: Rolf Findeisen**
16:00 – 16:35	**MUSTAFA KHAMMASH** ETH Zürich, Switzerland Opto-Cybergenetics: A Tango of Beams and Genes
16:35 - 17:10	**GREGORY BATT** Research Institute Pasteur Paris, France Adding automation and reactiveness to your experiments: motivation, tools and applications to cybergenetics
17:10 – 17:25	**ALEXANDER GRÄWE** TU Eindhoven, The Netherlands Not all is evil on the dark side – auto-inhibitors for luminescent virus biosensors
17:25 - 17:50	Centre Award/ PhD Price GFGSB - Short Presentation PhD Prices
18:00 - 20:00	Poster Session with beer

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International Synthetic Biology Workshop

Program 21 March 2023

The Sense-Compute-Response Paradigm

Session III	**Chair : Ulrike Nuber**
FLOW FOR LIFE	
9:00 - 9:35	**BRITTA TRAPPMANN** University of Münster, Germany Bioactive materials to probe cell-matrix interactions
9:35 - 10:10	**JAMIE DAVIES** Edinburgh, UK Creation of shape as a response effector
10:10 - 10:25	**SOURIK DEY** Leibniz INM Saarbrücken, Germany Thermoresponsive living therapeutic materials
10:25 - 10:35	CompuGene Student Lab/ SensUS
10:35 - 11:00	Coffee Break
Session IV	**Chair : Dominik Niopek**
Technological Advances	
11:00 - 11:35	**KATE ADAMALA** University of Minnesota, USA Synthetic biology taken to its logical conclusion: synthetic cells
11:35 - 12:10	**VITOR MARTINS DOS SANTOS** Wageningen University, Netherlands Towards autonomous biomanufacturing
12:10 - 12:45	**ROBERT TAMPE** University Frankfurt, Germany In-situ Receptor Organization and Signaling by Light
12:45 – 13:20	**CYNTHIA SHARMA** Würzburg University, Germany Non-coding RNAs in bacterial pathogens - from fundamental research to biomedical applications
13:20 - 14:30	Lunch & Poster Session
13:45 - 14:30	Mitgliederversammlung gFG
Session V	**Chair : Christina Weinberg**
Novel Sensing Devices	
14:30 - 15:05	**BARBARA DI VENTURA** Universität Freiburg, Germany The good, the bad and the intein
15:05 - 15:40	**ANDREAS MÖGLICH** University Bayreuth, Germany Optoribogenetics - The control of RNA by light
15:40 - 16:15	**JÖRG HARTIG** University Konstanz, Germany Novel Approaches for developing synthetic RNA Switches of Gene Expression
16:15 - 16:30	**ADAM MOL** University of Edinburgh, UK Development of novel RNA-based regulators for mammalian engineering biology
16:30 – 17:00	Coffee Break & Group Picture
17:00 – 18:00	SynBio Plenary Discussion
19:00	Conference Dinner

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The Sense-Compute-Response Paradigm

Session VI **Biomaterials**	**Chair: Matias Zurbriggen**
9:00 - 9:35	**WILFRIED WEBER** Leibniz INM - Leibniz and University of Saarland, Saarbrücken, Germany Programming Materials with Synthetic Biology
9:35 – 9:50	**TSVETOMIR IVANOV** MPI Mainz, Germany Adaptive multi-compartmentalized microreactors obtained by oleyl alcohol-assisted polymersome assembly
9:50 - 10:25	**OSKAR STAUFER** Leibniz INM Saarbrücken, Germany Bottom-up assembly of artificial tumor immune microenvironments
10:25 - 11:00	**ANNE S. MEYER** University of Rochester, USA DIY 3D printing of complex living materials for degrading bioplastic
11:00 - 11:30	Coffee Break
Session VII **Cell Free Synthetic Biology**	**Chair: Heinz Koeppl**
11:30 – 12:05	**HENRIKE NIEDERHOLTMEYER** TU Munich, Germany Engineering life-like systems from the bottom up
12:05 - 12:40	**SEBASTIAN MAERKL** EPFL, Switzerland On biochemical constructors and synthetic cells
12:40 – 12:55	**SCOTT SCHOLZ** MPI Marburg, Germany Genetic context can silence genes in bacteria and cell-free systems
12:55 - 13:30	**PAUL FREEMONT** Imperial College London, UK Cell-Free Expression: A strategy for prototyping parts, pathways, xenobiotics and complex systems
13:30 – 13:45	Concluding Remarks

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Short Talk Abstracts

Scott Scholz
Department of Biochemistry & Synthetic Metabolism, Max Planck Institute for Terrestrial Microbiology, Marburg, Germany

Genetic context can silence genes in bacteria and cell-free systems

Even in organisms with very information-dense genomes, such as E. coli, gene expression is heavily influenced by chromosomal position. Recently, we demonstrated that low genomic GC content flanking a gene, which is entirely outside of the promoter region and other canonical control elements, can cause silencing. These findings have implications for synthetic biologists seeking to design genetic pathways and circuits. Now, by testing reporter constructs in minimal cell-free expression systems, we also observe strong effects from flanking sequences. This suggests that so-called "xenogenic silencers" may not be entirely responsible for silencing observed on bacterial chromosomes, and a biophysical basis for genetic context effects, which may be present in many organisms.

Christoph Diehl
Department of Biochemistry & Synthetic Metabolism, Max Planck Institute for Terrestrial Microbiology, Marburg, Germany

Machine learning guided optimization of new-to-nature CO2-fixation cycles

In 2016 Schwander et al. published a new-to-nature pathway to fix CO2 to circumvent one of the bottlenecks of photosynthesis, the Ribulose-1,5-bisphosphate carboxylase oxygenase (RuBisCO). This pathway is founded on the Crotonyl-CoA carboxylase/reductase (Ccr), which belongs to the class of Enoyl-CoA carboxylase/reductases (Ecrs) among which are some of the fastest carboxylases known to date. This pathway, named the crotonyl-coenzyme A (CoA) /ethylmalonyl-CoA/hydroxybutyryl-CoA (CETCH) cycle, is more efficient than natural aerobic CO2-fixation pathways and harbors therefore the possibility to play an important role in the reduction of atmospheric CO2 levels (Schwander et al., 2016). To gain more insight of this complex in vitro assay of 27 components, we established a workflow to test hundreds of CETCH assays in parallel in vitro, allowing us to screen more than a thousand conditions. Prerequisite was the implementation of an acoustic liquid handler with a minimal pipetting volume of 25 nl. This enabled a high throughput by two factors: Pipetting speed and volume. While downscaling to 10 µl assays was crucial in terms of resources, e.g. purified enzymes, pipetting speed was essential since each round of 125 assays in triplicates consists of >10.000 pipetting steps. This data was used to iteratively train an XGBoost based machine learning algorithm to optimize the CETCH cycle to produce up to 2870 µM glycolate starting from 100 µM propionyl-CoA, which is more than ten times more efficient than the original version published in 2016.

Alexander Gräwe
Eindhoven University of Technology, Netherlands

Not all is evil on the dark side – auto-inhibitors for luminescent virus biosensors

The global human and animal populations are constantly threatened by viruses, in particular new virus variants that spread faster or adapt to new hosts. A fast way to counter potential epidemics is testing at the point of care using homogeneous one-step assays that do not require specialized equipment. In this regard, new bioluminescent sensor platforms show great potential for homogeneous analyte detection. Sensor proteins based on intramolecular complementation of split NanoLuc (NanoBiT) are particularly attractive because their modular design allows systematic tuning of sensor properties. We recently developed single component, biomolecular switches with a strongly reduced background signal for the detection of three clinically relevant antibodies by introducing catalytically inactive variants of the SmBiT subunit (DarkBiTs) as intramolecular inhibitors. Here, we show that this design can be adapted for detection of virus surface proteins like hemagglutinin and neuraminidase. The platform has potential to detect intact, infectious virus particles.

International Synthetic Biology Workshop

Short Talk Abstracts

Sourik Dey
Leibniz Institute for New Materials, Saarbrücken, Germany

Thermoresponsive living therapeutic materials - Darobactin-releasing bacterial hydrogels for treating chronic pathogenic infections

Targeted drug delivery through engineered microorganisms is a rapidly growing approach due to the extensive versatility of synthetic biology tools. Several beneficial bacteria are currently being used as a safe microbial chassis for developing sustainable drug production platforms. Our focus is to engineer an endotoxin free strain of E.coli to release a potent antimicrobial, Darobactin, to selectively eliminate Gram-negative pathogens. Darobactin production is regulated by an externally applied and sharply controlled temperature trigger for the sustainable use of engineered living therapeutics at diverse sites in the host anatomy. Peripherally induced heating can activate and maintain the drug production above the normal physiological temperature of 37oC with a high order fold change. The engineered bacteria will be securely encapsulated in biocompatible hydrogels to protect the bacteria from harsh conditions in the body, while preventing their escape to the surrounding tissues. The long-term sustenance and temperature induced drug release of the bacterial populations in hydrogels can act as an advanced therapeutic strategy to complement the existing treatment methodologies and provide better resolutions in eliminating chronic pathogenic infections.

Tsvetomir Ivanov
Department of Physical Chemistry of Polymers, Max Planck Institute for Polymer Research, Mainz, Germany

Adaptive microreactors obtained by oleyl alcohol-based polymersome assembly

Compartmentalization is an essential feature of cells. The ability to control the formation, distribution, and function of compartments is essential for life. In recent years, polymersomes have emerged as viable synthetic compartments for basic and applied studies of synthetic cells. Their chemical versatility and robustness make them stable compartments. However, due to the usually high molecular weight of the blocks used to make them, polymersomes are characterized by thick, non-permeable membranes that limit their application as biomimetic compartments. In this study, we developed a novel minimal microfluidics method to prepare monodisperse semipermeable polymersomes. The polymeric compartments were prepared without the addition of surfactants by using low molecular weight diblock copolymers as membrane components. We have shown that low molecular weight polymers can play the dual role of surfactant and membrane component when a suitable organic phase is used in the formation of double emulsion droplets by microfluidics. The developed method allowed the preparation of monodisperse polymersomes within only one minute at high throughput. The versatility of the low molecular weight polymersomes was demonstrated by their application as biomimetic compartments in the construction of cell-like microreactors. The microreactors were based on the encapsulation of biomolecules and pH-sensitive coacervate droplets. The method described in this contribution provides a versatile platform for the development of polymer-based cell-like systems, such as delivery systems, bioreactors, and synthetic cells.

International Synthetic Biology Workshop

Short Talk Abstracts

Dora Tang
Max Planck Institute for Cellular Molecular Biology and Genetics, Dresden, Germany

Feedback communication in populations of synthetic cells

One of the grand challenges in synthetic biology is to build and control synthetic cell populations with increasing levels of molecular complexity. In biology, multicellular systems use communication via sense and response mechanisms to coordinate cells across length scales. Thus, the controlled production of synthetic cells with sense and response mechanisms are critical for rational production of multicellular systems. A bottom-up approach allows us to replicate key biological processes using a small number of basic building blocks. This methodology has the added advantage that properties and characteristics of a synthetic cell can be readily tuned and adapted.

Here, I will present strategies for the production of synthetic cellular compartments that contain cell free gene expression with controlled heterogeneity. Further to this, I will discuss our capabilities to integrate cell free gene circuits that have feedback mechanisms into compartments separated by droplet interface bilayers. This provides a strategy to implement sense and response mechanisms within populations of cells. Our results show that we are able to fabricate synthetic compartments using microfluidics and liquid handling devices with high levels of control. Together, our work provides a step towards building more complex multicellular systems which can sense and respond, from the bottom-up.

Adam Mol
UK Centre for Mammalian Synthetic Biology, Centre for Engineering Biology, Institute of Quantitative Biology, Biochemistry, and Biotechnology, School of Biological Sciences, The University of Edinburgh, Edinburgh, United Kingdom

Development of novel RNA-based regulators for mammalian engineering biology

For many engineering biology applications, fine-tuning of gene expression is critical. Mammalian regulatory tools use diverse mechanisms to allow flexible, precise, and comprehensive control over gene expression and cellular development. More recently, RNA-based regulatory devices have been explored for modulating mammalian gene expression. Due to their structural properties, riboregulators provide a convenient basis for the development of ligand-dependent controllable systems. In this project, we developed novel aptazyme switches for the control of gene regulation with potential application in e.g. construction of mammalian synthetic circuits. In mammalian systems, insertion of aptazymes in the 3' untranslated region of the mRNA of the gene have been utilized for controlling gene expression on a post-transcriptional level. Aptazymes can be engineered by attaching ligand-sensing aptamer domain to the catalytically active ribozyme. Ligand-responsive ribozyme switches can regulate self-cleavage events in mRNAs to modulate the stability of the transcript in response to ligand levels. The utilization of aptazymes in engineering biology and therapeutic applications has many advantages such as an increased robustness due to in cis regulation, small coding space and a high degree of modularity. In this project, we developed a novel ON- and OFF- switching aptazyme platform in mammalian cells by using a rational-design approach. Our aptazyme is composed of the hammerhead ribozyme, derived from satellite tobacco ringspot virus and a synthetic RNA aptamer, that can bind to the bacterial Tet repressor. The aptazymes display very low basal expression and a high fold conversion of a reporter gene expression in mammalian cell culture. The fold induction obtained in our study represents a major improvement compared to existing aptazyme-based devices in mammals. Therefore, our system not only opens new opportunities for practical applications of gene regulatory systems, but also expands the scope of Tet-systems prevalent in the field of engineering biology.

International Synthetic Biology Workshop

Poster Abstracts

1. Jan Kalkowski and Franka Eiche
Max Planck Institute for Terrestrial Microbiology, Marburg, Germany

On-chip generation of reaction compartments for the screening of protein libraries in ultrahigh-throughput

The use of engineered proteins with improved or altered properties, e.g. in their enzymatic activity or in their binding partners, is an essential part of modern biotechnological applications. The screening of protein libraries to identify variants with the desired properties is laborious and the bottleneck in many engineering projects. A frequently used method to select protein variants of interest is to couple the protein's function with the generation of a fluorescent signal so that variants with improved characteristics can be screened for in plate reader assays or even selected in ultrahigh-throughput by fluorescence-activated cell sorting (FACS). But plate reader assays have limited throughput and FACS screening is not always favorable as it only works with intact cells, therefore membrane impermeable substrates and cofactors (e.g. CoA thioesters, NAD(P)H and ATP) cannot be externally added and their interaction with the protein of interest assessed. Water-oil-water double emulsion droplets encapsulating cell-free expression systems are an interesting alternative approach for genotype-phenotype coupling. Here, we show the generation of double emulsion droplets by a simple two-step process in which water-oil droplets are formed on a microfluidic chip, which are subsequently re-emulsified by vortexing in an aqueous carrier solution. Afterwards the double emulsion droplets will be sorted via FACS and the genotype can be recovered by PCR after breakage of the droplets. We aim to use this method for the engineering of glycolyl-CoA carboxylase (GCC), a new-to-nature enzyme of the tartronyl-CoA (TaCo) pathway, by either screening for NADPH reduction in a coupled enzymatic assay or the direct detection of the product tartronyl-CoA by a biosensor.

2. Martine Ballinger and Elizaveta Bobkova
Max Planck Institute for Terrestrial Microbiology, Marburg, Germany

Assessment of antimicrobial peptides and Transcription and Translation in Giant Unilamellar Vesicles

Giant unilamellar vesicles (GUVs) are 1-130 um diameter aqueous droplets, separated from the surrounding solution by a lipid bilayer. Through their simple structure, they offer a powerful tool for mimicking and investigating cell membrane interactions with its surroundings. Furthermore GUVs facilitate development and testing of new to nature entities, such as novel antimicrobial peptides (AMPs) or engineered transmembrane proteins. In this work, we discuss arraying GUVs and imaging them over time, so that AMPs can be screened and their mode of action determined. Furthermore, we have established methods for encapsulation of transcription-translation reagents (TX-TL) into uniform GUVs produced using microfluidics and an optimised TX-TL mixture. This allows the production of proteins inside GUVs in close proximity to the membrane, thus circumventing the need to separately produce, purify and reconstitute certain membrane-interacting proteins of interest. Higher-throughput screening of protein variants could then be done, for example by encapsulation of single variants of membrane-interacting protein genes into GUVs, and subsequent selection of promising variants, based on binding assays or FACS sorting.

Poster Abstracts

3. Jan Mathony[1,2], Sabine Aschenbrenner[1,2], Dominik Niopek[1,2]
[1]Center for Synthetic Biology, Technical University of Darmstadt, Darmstadt, Germany; [2]Department of Biology, Technical University of Darmstadt, Darmstadt, Germany

Structural and functional constraints of domain insertion engineering

Engineered allosteric protein switches that react to triggers such as light or small molecules represent powerful tools for basic research and biotechnology. They enable customized control over protein activity by harnessing switchable domains and functionally linking them to effector proteins. The insertion of light-responsive receptor domains into an effector protein of choice, for instance, can enable the control of effector activity with light. Unfortunately, little is known about the structural and biophysical requirements for successful domain insertions, so that the design of protein switches still relies on trial and error by extensive testing of variants. In order to systematically investigate possibilities and constraints of protein engineering by domain insertion, we inserted up to five structurally and functionally unrelated domains into several different candidate effector proteins at all possible positions. The resulting libraries of protein hybrids were screened for activity by fluorescence-activated cell sorting (FACS) and subsequent next-generation sequencing (Flow-seq). Training machine learning models on the resulting, comprehensive datasets allowed us to dissect parameters that affect domain insertion tolerance and revealed that sequence conservation statistics are the most powerful predictors for domain insertion success. Finally, extending our experimental Flow-seq pipeline towards the screening of engineered, switchable effector variants yielded two potent optogenetic derivatives of the E. coli transcription factor AraC. These novel hybrids enable the co-regulation of bacterial gene expression by light and chemicals. Taken together, the generation of a large domain insertion datasets enabled - for the first time - the unbiased investigation of domain insertion tolerance in several evolutionary unrelated proteins. Our study showcases the manifold opportunities and remaining challenges behind the engineering of proteins with new properties and functionalities by domain recombination.

4. Sebastian Barthel, Luca Brenker, Christoph Diehl
Max Planck Institute for Terrestrial Microbiology, Marburg, Germany

Prototyping complex metabolic pathways using in vitro transcription

Until recently, the Design-Build-Test-Learn (DBTL) cycle in metabolic engineering was limited by the construction of microbial strains, which encode a variant of the metabolic pathway of interest. With the rise of cell-free expression system in metabolic engineering, mixing and matching of enzyme, substrate and cofactor identities and concentrations in vast combinatorial spaces became feasible with minimal time investment per sample. The rate-limiting step of the DBTL cycle consequently shifted to the analysis of samples, e.g. via liquid chromatography-mass spectrometry (LC-MS). To further accelerate DBTL cycles, save money on consumables and reduce the use of toxic solvents, we propose the use of in vitro transcription (IVT)-based biosensing like the previously published RNA Output Sensors Activated by Ligand Induction (ROSALIND) system for the fast and cheap screening of metabolic pathways. ROSALIND is easily adaptable to other metabolites of interest by exchanging the respective transcription factor-operator pair, given that a suitable transcription factor exists. We therefore constructed and characterized a glycolate biosensor based on the transcription factor Pden4400 from Paracoccus denitrificans, and critically assessed the possibility to transition a system that was originally developed for quality control of purified water samples for the prototyping of complex metabolic pathways such as the synthetic CO2-fixing CETCH cycle (27 components). For the latter, we used previous results on the optimization of the CETCH cycle to search for boundaries of this screening concept, e.g. sources of IVT inhibition or sensor promiscuity.

Poster Abstracts

5. Markus Meier, Scott A. Scholz, Tobias J. Erb
Max-Planck-Institute for Terrestrial Microbiology, Marburg, Germany

A Genetic Module for In Vitro Membrane Protein Integration

Membrane proteins are essential elements of life, equipping biomembranes with diverse functions like mechanical strength, selective transport, energy production and signal transduction. However, their hydrophobicity and natural requirement for insertion machineries impede their broad use outside of living cells. Thus, despite their high potential for academic and technological applications, membrane proteins are underrepresented in vitro. We are developing a simple tool to facilitate the directional insertion and functionality of membrane proteins in vitro. By combining cell-free protein synthesis with a genetic module for the E. coli Sec system, we can promote the translocation of a co-expressed reporter. Currently, we are testing and optimizing the system to enable functionality of different multi-pass transmembrane proteins. Since E. coli is the most widely used host for protein production, we hope future iterations of our E. coli-based module will enable a variety of in vitro applications for membrane proteins.

6. Daniel Kelvin, Beatrix Suess
[1]Center for Synthetic Biology, Technical University of Darmstadt, Darmstadt, Germany; [2]Department of Biology, Technical University of Darmstadt, Darmstadt, Germany

Synthetically engineered riboswitches as versatile regulatory devices

Modern synthetic biology has developed a variety of different devices to influence the regulation of gene expression in biological systems. A group of genetic elements known as riboswitches consist solely out of RNA and can bind to a designated ligand with high specificity and affinity. These devices possess the ability to regulate gene expression through different mechanisms such as translation initiation, pre-mRNA splicing or RNA self-cleavage. Regulation is driven through changes in the tertiary structure of a riboswitch facilitated by ligand binding, which occurs without the need for any auxiliary factors. Due to these properties riboswitches are excellent candidates for the creation of ligand-controlled genetic circuits. Here we present different synthetically engineered riboswitches, which have been discovered through a process known as the Synthetic Evolution of Ligands by Exponential Enrichment (SELEX) and further optimized to function as regulatory devices. By engineering these devices we aim to provide new tools for the study of complex regulatory systems, as well as the design of synthetic metabolic pathways and biosensors.

1.

7. Rohita Roy
Indian Institute of Technology, Bombay, India

Development of a palette of fluorescent whole cell biosensors for aromatic pollutant detection in drinking water sources

Environmental monitoring related to water contamination has been one of the global priorities due to the crucial juxtaposition between human health and socio-economic development. The increased momentum of urbanization and industrialization has led to an unregulated release of industrial effluents, eventually jeopardizing the safety and availability of clean drinking water. Thus achieving universal and equitable access to drinking water necessitates the development of a simple and inexpensive tool for water quality monitoring. Aromatic compounds such as phenols, benzene, and toluene and its derivatives are carcinogenic xenobiotics that are known to pollute water resources and therefore their persistence in the environment is of great concern. Inherently, the MopR genetic system from the soil bacteria Acinetobacter sp. can sense and degrade phenol. By the combinatorial approach of structure-guided design and synthetic biology tools, we have exploited the existing MopR system to create a tunable array of whole-cell biosensors (WCBs) which can quantitatively and specifically detect the presence of these pollutants. We have reported detection sensitivity down to ~1 ppb, by using a single sensor module engineered with mutations to enable the generation of an array of biosensors towards benzene and its derivatives without losing sensitivity. Apart from multiplexing the sensor module, we have tailored the reporter gene chromophoric unit so as give different colored emission output on specifically recognising the aromatic ligands.Thus, we have developed a palette of fluorescent biosensor with capability of water quality monitoring and detecting a plethora of aromatic pollutants even in a mixture of compounds.

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Poster Abstracts

8. Lisa-Marie Maurer[1,2], Michael P. Vockenhuber[1,2], Yves A. Muller[3] and Beatrix Suess[1,2]
[1]Department of Biology, TU Darmstadt, Darmstadt, Germany, [2]Centre for Synthetic Biology, TU Darmstadt, Germany [3]Division of Biotechnology, Department of Biology, Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany

Protein-binding RNA aptamers as versatile tools for genetic circuits

Genetic circuits as part of synthetic biology are widely used and have opened a playfield for complex in vivo regulations in cells. RNA aptamers as a part of genetic circuits open up the possibility to work with regulators its ligands are toxic to cells. A prominent example of this is the aptamer for the transcription factor TetR (Hunsicker et al. 2009). The TetR aptamer is a versatile tool that can induce the expression of TetR-controlled genes as well as function as part of a splicing device (Mol et al. 2019). Another repressor protein CymR like TetR a transcription factor and for this a great target for an in vitro aptamer selection via SELEX (Systematic Evolution of Ligands by EXponetial enrichment). SELEX as a tool for the enrichment of binding sequences to a distinct target provides then a potential target binding sequence pool. To analyze an enriched sequence pool for in vivo binding a corresponding screening system is needed. For this, we choose a two-plasmid screening system with a low and a high copy plasmid containing the target protein, its operator, and the pool sequences as well as GFP as a reporter gene. With this system, we can perform a high throughput screening for aptamers that interfere with protein-DNA binding. Here the first results of the CymR aptamer screening are shown

9. Janis Hoetzel[1,*], Claire Husser[2,*], Michael Ryckelynck[2], Beatrix Suess[1,3] * contributed equally
[1]Department of Biology, Technical University of Darmstadt, Germany [2] Université de Strasbourg, CNRS, Architecture et Réactivité de l'ARN, France [3] Center for Synthetic Biology, Technical University of Darmstadt

Development of Inhibitory RNA Aptamers against Metallo-β-lactamases

The increasing occurrence of antibiotic-resistant bacteria is a growing threat for the public health worldwide. Combined with big pharmaceutical companies leaving the field of antibiotic compound development, bacterial infection could become the number one cause of death by 2050. To address this growing threat, we designed a high-throughput pipeline for the development of inhibitory RNA aptamers against proteins (DIRA). The pipeline consists of two parts: an initial screening for binding affinity via systematic evolution of ligands by exponential enrichment (SELEX) and a subsequent microfluidic screening for enzymatic activity which selects for inhibitory capabilities of the RNA sequences. The combination of these methods allows for a fast and effective development of inhibitory RNA aptamers against any given protein. Since bacteria expressing metallo-β-lactamases are particularly difficult to treat, we selected the Sao Paolo metallo-β-lactamase 1 (SPM-1) as the first target for our pipeline. First, we started with a randomized RNA pool and obtained an enriched pool of target-binding sequences. Second, we further selected the pre-selected pool for inhibition of the target protein activity via the microfluidic pipeline. After the first complete run through the pipeline, we obtained a highly enriched sequence that proved to bind SPM-1 with high affinity (89,8 ± 10,4 pM) and effectively inhibited the protein activity. The sequence was further characterized and reduced to a minimal binding motif that was only 37 nucleotides long and still served as an effective inhibitor. In the next step this minimal aptamer will be linked to a bacterial siderophore and tested for its *in-vivo* efficiency. With the functional minimal aptamer, we have proven the effectiveness of our pipeline and are theoretically capable of quickly developing inhibitory RNA aptamers against any given protein

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Poster Abstracts

10. Arsen Korpetayev[1,2], Beatrix Suess[1,2]
[1]Department of Biology, TU Darmstadt, Darmstadt, Germany, [2]Centre for Synthetic Biology, TU Darmstadt, Germany

With ultra-competent E.Coli reaching transfected library size of 108, Liu and colleagues (https://doi.org/10.1021/acssynbio.8b00099), managed to select for a de-novo aptamer domain in-vivo. Now we are trying to employ in-vivo diversification to exceed the limit of transfection efficiency to obtain higher library size for de-novo aptamer selection in-vivo. For that end we are reengineering EvolvR to reach higher mutational frequency, which is only around 1% in the original EvolvR fusion.

11. Aukse Gaizauskaite[1], Henrike Niederholtmeyer[1,2]
[1]Max Planck Institute for Terrestrial Microbiology, [2]Technical University of Munich, Germany

Engineering Biomolecular Condensates in Cell-Free Systems

Several proteins, that have intrinsically disordered regions (IDRs) and high multivalency, possess the ability to self-associate into molecularly crowded liquid-like droplets, so called biomolecular condensates. In nature, living cells employ condensates as membranelles organelles for spatial organisation, which allows effective separation of chemical reactions, concentration of molecules, and regulation of reaction kinetics. Cell-free transcription and translation (TX-TL) systems have emerged as alternatives to living cells in bioengineering, but they are still lacking ways to compartmentalise molecules. In our approach, microfluidic techniques and specifically designed microfluidic devices are applied to characterise and engineer protein-condensates in cell-free systems. Micrometre size environments in microfluidic chips with diffusive supply of TX-TL reagents ensure long-term continuous protein synthesis with the constant supply of fresh reaction components. Synthetic protein condensates, as programmable and dynamic molecular assemblies, can be useful for the construction of life-like systems from the bottom up, as well as for the creation of biochemically active compartments by programming the sequestration of different molecules or signalling networks.

12. Francois-Xavier Lehr, B Pavletić, T Glatter, T Heimerl, R Moeller, Henrike Niederholtmeyer
Max Planck Institute for Terrestrial Microbiology / LOEWE Zentrum Synthetische Mikrobiologie Marburg, Germany

Enhanced assembly of bacteriophage T7 produced in cell-free reactions under simulated microgravity

Viruses and virus-like particles are fascinating multi-protein structures capable of self-assembly. Their bottom-up construction in cell-free transcription-translation (TXTL) reactions provides new possibilities to better understand their fundamental mechanisms as well as offering new means of production for promising therapeutics. Here, we show how TXTL systems were used to study the effect of simulated microgravity on the synthesis and assembly of the model bacteriophage T7. Rotation in a 2D-clinostat increased the number of infectious T7 particles compared to static controls. Quantitative analyses by mass spectrometry, immuno-dot-blot and real-time PCR showed no significant differences in protein and DNA contents, suggesting enhanced self-assembly of T7 phages in simulated microgravity. Additionally, we compared the TXTL synthesis kinetics of T7 bacteriophages with infection in living cells. Using time-resolved proteomics, we detected up to 90% of the phage proteins and analyzed their time-dependent expression profiles in TXTL systems and living cells.

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Poster Abstracts

13. T. Ingenhaag[1], F. Theillet [2], A. Löwer[1]
[1]Technische Universität Darmstadt, Department of Biology, Darmstadt, Germany, [2]Centre National de la Recherche Scientifique, Institut de Biologie Intégrative de la Cellule, Gif-sur- Yvette, France

Regulation of the DNA-damage response by phosphorylation clusters in the p53 signaling network

The transcription factor p53 coordinates the cellular response to DNA damage. P53 protein level and activity are highly regulated by a signaling network comprising the DNA damage response kinases ATM/ ATR/ DNA-PK (PIKKs), the kinase Chk2, the E3-ubiquitin ligase Mdm2 and the phosphatase PPM1D/Wip1. The activity of the kinases/phosphatases and reciprocal feedbacks generate repeated p53 accumulation pulses, whose duration and number determine p53-mediated transcriptional responses and cell fate. Interestingly, Chk2 and Mdm2 contain clustered phosphorylation sites of PIKKs (SQ/TQ motifs). Since multisite phosphorylation can intricately regulate protein function, we hypothesized that these additional phosphosites act as a buffer to set thresholds and molecular timers for modification of key regulatory residues upon DNA damage. Therefore, multisite phosphorylation could fine-tune Mdm2 and Chk2 activity and thereby regulate the p53 network and its long-term dynamics. By using Cas9-mediated genomic engineering, we established breast epithelial cell lines with mutations in several SQ/TQ motifs in the N-terminal domain of Chk2. Time-lapse live-cell imaging indicates that these phosphosite mutations affect Chk2 activation, leading to higher basal p53 levels and altered timing of p53 pulses upon DNA damage. To gain further insights into this regulatory mechanism, we will elucidate how mutations in SQ/TQ motifs affect phosphorylation kinetics of the remaining phosphosites in Chk2 by using NMR spectroscopy. Furthermore, we will monitor the consequences of these mutations on p53 dynamics, target gene expression and cellular outcome. Our aim is to examine the functional role of individual phosphosites in the p53 network and to evaluate how the balance between PIKK, Chk2 and Wip1 activities shapes p53 dynamics.

14. Yiğitcan Sümbelli[1], Alexander F. Mason[2], Jan C.M. van Hest[1]
[1]Department of Biomedical Engineering, Chemical Engineering and Chemistry, Institute for Complex Molecular Systems, Eindhoven University of Technology, The Netherlands [2] School of Biotechnology and Biomolecular Science, University of New South Wales, Sydney NSW, 2052, Australia

Communication within Artificial Cell Mediated Tissue Engineering

Artificial cell-mediated tissue engineering approaches have started to gain interest to study the translational applications of synthetic cells in regenerative medicine studies. 3D bioprinting is a versatile technique for this purpose as it allows to combine artificial cells along with biomaterial inks into an engineered final product which can mimic the biological and physicochemical properties of natural tissues. In this study, a communication pathway was set up within a 3D-printed scaffold. Terpolymer stabilized amylose-coacervates as artificial cell models were embedded into methacrylated gelatin and poly(ethylene glycol) diacrylate (PEGDA) based biomaterial ink formulation to fabricate artificial tissue models. The model cargo protein was sequestered by the coacervate population via a DNA-mediated uptake mechanism with a subsequently triggered release behavior within the 3D-printed scaffolds. The cross-linking degree and the swelling behavior of the scaffolds were studied along with fluorescence recovery after photobleaching (FRAP) studies to evaluate the diffusion behavior of the cargo molecules.

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Poster Abstracts

15. Sebastian Köbbing[1], Lars M. Blank[1], Nick Wierckx[1,2]
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Identification of reliable genomic landing sites for heterologous constructs in Pseudomonas putida KT2440

Genomic integration tools based on transposons or homologous recombination are commonly used to generate stable production hosts. Microbial chassis design usually relies on numerous genomic integrations for heterologous gene expression. However, so far for many microbial workhorses only very limited numbers of suitable integration sites were characterized, thereby restraining advanced genome engineering. Here, we report on the identification of novel genomic integration sites, so-called landing pads, for P. putida KT2440, an ever more established microbial chassis used for challenging biocatalytic applications. From a collection of RNA-Seq data covering different carbon sources, and temperatures, we identified genomic regions with expression pattern that were constant under all tested conditions. These sites are potential landing pads allowing condition-independent gene expression. This study characterized ten potential landing pads using four different msfGFP expression cassettes. In addition, an insulated probe sensor was used to study recombinant gene expression under changing cultivation conditions. The identification and comparative characterization of all landing pads showed that the msfGFP signal varied between the different sites, indicating a strong influence of the genomic context. Therefore, the effect of the genomic context is an additional parameter that must be considered in the design of integrable genomic cassettes for tailored heterologous expression. The here presented set of characterized genomic landing pads increases the genetic tool set for stable heterologous gene expression by chromosomal integration, thereby enabling advanced metabolic engineering of P. putida KT2440 that is independent from expression plasmids.

16. Johannes Seifert
Forschungszentrum Jülich GmbH, Jülich, Germany

From microbial sensing to insight and control - the power of machine learning for automating live-cell imaging workflows

Modern microfluidic lab-on-chip devices enable the parallel cultivation of microbial populations in highly controlled environments of picoliter-sized bioreactors. Combined with automated live-cell microscopy and fluorescence biosensors, the technology allows performing spatio-temporal sensing with single-cell resolution. Thus, observing cellular development, intracellular processes, growth patterns, and cell-to-cell interactions for various microbial organisms, including bacteria such as E. coli, C. glutamicum, fungi, or algae, is achievable. Extracting valuable biological information from recorded images requires the computational processing of millions of cells per experiment to arrive at reliable and reproducible results. This leads to tremendous challenges for automating the recognition of individual cells (segmentation) and following their precise development through time (tracking). In addition, statistical methods are required to analyze the information. In practice, the scientific and interdisciplinary microbial research domain also demands high flexibility, usability, and scalability throughout the complete analysis process. To address these challenges, we present the open-source ObiWan-Microbi platform designed for highly automated analysis workflows paired with collaborative, user-friendly, and FAIR data management. It provides powerful tools to adapt machine learning segmentation and tracking to custom imaging setups and across microbial morphologies using interactive user interfaces. In combination with remote computation triggered from customizable analysis notebooks, ObiWan-Microbi meets the demands of collaborative research while maintaining speed, robustness, flexibility, and user-friendliness. We challenge the software's analysis capabilities at the example of a highly automated analysis for an auxotrophic microbial co-culture. The digitization of microfluidic lab-on-chip systems allows dynamic control of environmental parameters, including medium, gas, light, and temperature. Combined with precise, customizable, and real-time capable analysis of microscope images, the technological foundation for detecting specific events on the single-cell level is available. These detected events can then trigger tailored response actions. Application scenarios range from dynamic imaging and quality control to dynamic environment modifications based on the cell colony size and complete control of cellular growth and production. The joint application of high-resolution sensing using automated microscopes and adaptable machine learning analysis workflows unlocks the potential of intelligent response triggering in microfluidic imaging on the level of individual cells and opens a new dimension for microfluidic single-cell analysis.

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Poster Abstracts

17. Iris Eckert[1], Richard Friedrich[2,3], Zasha Weinberg[1,*], Christina E. Weinberg[2]
[1]Bioinformatics Group, Department of Computer Science and Interdisciplinary Centre for Bioinformatics, Leipzig University, Germany, [2]Institute of Biochemistry, Leipzig University, Germany, [3]AlphaOmega Labor, Leipzig, Germany

Discovery of natural non-circular permutations in non-coding RNAs

Possibly one of the most intriguing facets of RNA is its ability to catalyze chemical reactions. Examples of such catalytic RNAs, called ribozymes, can be found in nature and have been selected in the test tube. In synthetic biology, ribozymes are used alone or as modular building block for complex RNA-devices, for example to regulate gene expression in response to certain cellular signals. Flexibility in how to connect different RNA modules can enable novel and more-complex RNA regulatory devices. The fact that RNAs are known to occur in simple rearrangements of their structure that retain function might provide this needed flexibility. Circular permutations, in which the 5′ and 3′ portions of the molecule are exchanged, have been known for RNAs for decades. However, we recently bioinformatically identified the first natural examples of RNAs exhibiting non-circular rearrangements (permutations). We experimentally validated these naturally occurring RNAs that, at their core, represent permuted hammerhead ribozyme RNAs. We determined ribozyme cleavage speeds and evaluated the predicted RNA structure by investigating the cleavage activity of mutated ribozyme sequences. Our results further demonstrate the structural sophistication of RNA, and could be exploited in RNA-based biotechnology applications.

18. Carla Maneira, Alexandre Chamas, Gerald Lackner
Synthetic Microbiology Group, Leibniz Institute for Natural Product Research and Infection Biology - Hans-Knöll-Institute, Jena, Germany

Development of a multilayered biocontainment module for therapeutic yeasts

As the synthetic biology field lives a boom in the last decades, the employment of genetically modified organisms (GMOs) in the most diverse industrial and social applications becomes more concrete each day. The development of effective biocontainment strategies for restricting GMOs to their environments of action is of utmost importance to avoid the invasion of transgenes into the environment. In this context, there are many examples of robust biocontainment strategies designed for bacteria, but few are the approaches developed for yeast, especially in the context of genetically engineered live biotherapeutics (LBPs). In this work, we pursue the development of a genomically embedded multilayered biocontainment system for S. cerevisiae which relies on the presence of small edible molecules in micromolar concentrations and environmentally-restricted hints to control cellular processes and ultimately restrain cell growth to the gut. The biosafety system relies on different modes of action to ensure redundancy, namely, the control of essential genes' expression by transcription-factor-based biosensors, as well as the induction of lethality via genomic rupture - CRISPR-based kill switch - in addition to common auxotrophies. As a final aim, the complete multimodule biocontainment system should support a minimum escape rate of 10^-8 to comply with the NIH standards. Furthermore, parallel engineering of the commercially-available probiotic S. cerevisiae var. boulardii has been carried out in an effort to push forward probiotic LBPs.

Poster Abstracts

19. Yanez-Feliu Guillermo
Newcastle University, UK

Multicellularity and collective cell behaviour exemplify the emergence of complex patterns and structures across scales in living systems.

When cells interact, they can generate higher order patterns of gene expression to communicate and orchestrate development. There are a wide range of phenomena in which a key element to a biological process is the appearance of a traveling wave of chemical concentration, mechanical deformation, electrical or other type of signal. Thus, studying traveling waves is relevant to our understanding of fundamental mechanisms underlying information processing in pattern formation. Previously we have studied the coupling between a synthetic genetic oscillator, the repressilator [1], and constraints on cell growth in colonies via protein dilution. Our theory predicts that these mechanical constraints generate patterns of growth rate inhomogeneities in growing cell colonies, inducing the emergence of traveling waves of gene expression [2]. Based on this work, we derived a simple Partial Differential Equation that describes the system and generalizes to any genetic network. Furthermore, we used time-lapse fluorescence microscopy to show that colonies of bacterial cells carrying the repressilator circuit do indeed form traveling waves, supporting our predictions. This work demonstrates that mechanical constraints can give rise to higher order gene expression patterns in cell colonies and provides a simple system for their design and analysis. The understanding of complex multicellular behaviours at multiple scales in order to control how these patterns are generated and maintained will enable applications in areas such as embryonic development, tumour formation, wound healing, and tissue engineering. [1] Potvin-Trottier, L., et al. (2016). Synchronous long-term oscillations in a synthetic gene circuit. Nature 538, 514–517. [2] Yáñez Feliú, G., et al. (2020). Novel tunable spatio-temporal patterns from a simple genetic oscillator circuit. Frontiers in bioengineering and biotechnology, 893.

20. Mahnaz Sabeti Azad
INRAE Micalis

Cell-Free Protein Synthesis from Exonuclease-Deficient Cellular Extracts Utilizing Linear DNA Templates

Cell-free protein synthesis (CFPS) has recently become very popular in the field of synthetic biology due to its numerous advantages. Using linear DNA templates for CFPS will further enable the technology to reach its full potential, decreasing the experimental time by eliminating the steps of cloning, transformation, and plasmid extraction. Linear DNA can be rapidly and easily amplified by PCR to obtain high concentrations of the template, avoiding potential in vivo expression toxicity. However, linear DNA templates are rapidly degraded by exonucleases that are naturally present in the cell extracts. There are several strategies that have been proposed to tackle this problem, such as adding nuclease inhibitors or chemical modification of linear DNA ends for protection. All these strategies cost extra time and resources and are yet to obtain near-plasmid levels of protein expression. A detailed protocol for an alternative strategy is presented here for using linear DNA templates for CFPS. By using cell extracts from exonuclease-deficient knockout cells, linear DNA templates remain intact without requiring any end-modifications. We present the preparation steps of cell lysate from Escherichia coli BL21 Rosetta2 ΔrecBCD strain by sonication lysis and buffer calibration for Mg-glutamate (Mg-glu) and K-glutamate (K-glu) specifically for linear DNA. This method is able to achieve protein expression levels comparable to that from plasmid DNA in E. coli CFPS.

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Poster Abstracts

21. Alina Kuzembayeva[1], Jérémie Marlhens[1], Felix Reinhardt[1], Hendrik Cooper[1], Francois-Xavier Lehr[2], Heinz Köppl[1]
[1] Self-Organizing Systems Lab, TU Darmstadt, Centre for Synthetic Biology, TU Darmstadt, Germany, [2] Niederholtmeyer Lab, TU Munich

Engineering RNA-based Dynamic Logic Gates in TXTL System and E. coli

Due to their enormous advantages over protein-based circuits, RNA-based circuits controlling gene expression have great promise in synthetic biology. Two examples of these advantages are quick reaction times and reduced metabolic costs. Logic gates are the essential parts of the gene regulatory networks that cells utilize to cascade and incorporate various environmental and cellular signals and their responses. In response to specific signalling inputs, desirable behaviours can be generated and controlled. The gates were generated by combining a variety of short transcriptional activator RNAs (STARs) with Toehold switches. To evaluate the functionality of the logic gate components, an *Escherichia coli* (*E. coli*) and *E. coli* cell-free transcription-translation (TXTL) system was employed. Tests for a wide range of concentrations and construct designs were conducted using a TX-TL system with an Echo 525 Liquid handler and *E. coli* cells. One of the designs, feedforward loops (FFL), is capable of interpreting external signals and responding in a very particular and reliable way, either speeding up or delaying responses. They are common signalling motifs that speed up the response time of target gene expression following stimulus steps in one direction. RNA-based biosensors can be good diagnostic instruments. This presents a chance to develop quick, non-invasive clinical diagnostics for use in general practitioners' offices or hospitals.

22. Imre Banlaki and Henrike Niederholtmeyer
Max Planck Institute for Terrestrial Microbiology, Marburg, Germany.

Cell-mimics continuously communicate in 2D, supported by 3D microfluidic perfusion

Cell free transcription and translation provides a well-controlled environment to test gene regulatory networks and their products ex vivo. Gene regulatory networks distributed in communities of cell-mimics could lead to the formation of self-organized patterns in gene expression. To achieve this goal, it is necessary to increase the life-likeness of the cell free in vitro system using a continuous perfusion setup maintaining the reaction far from equilibrium. However, perturbations, from the feeding of fresh reagents, mix establishing concentration gradients in an unprotected reaction space. We present a multilayer, microfluidic chip separating the feeding flow from the protected, 2D reaction chamber. As cell-mimics, we use porous capsules, with immobilized DNA cargo in an internal, primary hydrogel, to distribute gene regulatory networks in a discrete 2D array. An external hydrogel immobilizes the capsules after arrangement and constitutes the reaction space. Overflowing the gel pad with reagents, creates a two-layer system with separated feeding and reaction spaces. This setup allows us to model communication between synthetic cells in two dimensions, a prerequisite for multicellular organization. Using this device, we aim to characterize increasingly complex gene regulatory networks, leading to dynamic and static self-organizing patterns.

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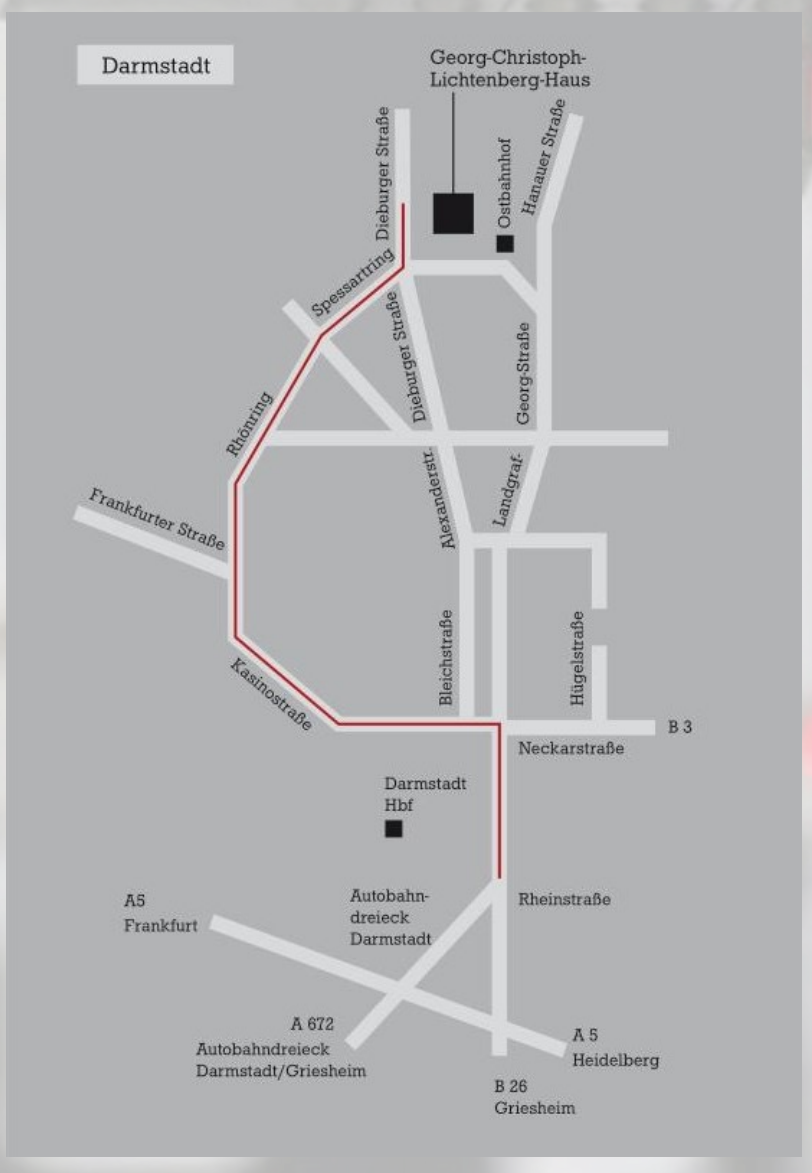
Georg-Christoph –Lichtenberghaus Haus

The Conference Dinner takes place at the Georg-Christoph Lichtenberghaus.

We provide a direct transfer by bus from the clock tower auditorium. But if you want to travel individually take bus line F from the “Schloss“, direction "Oberwaldhaus". Please get off at the bus stop "Fasanerie". The Georg-Christoph-Lichtenberg-Haus is located on the opposite side of the bus stop.

We recommend arriving by public transport, as there is only a limited number of parking spaces available in front of the Georg-Christoph-Lichtenberghaus.



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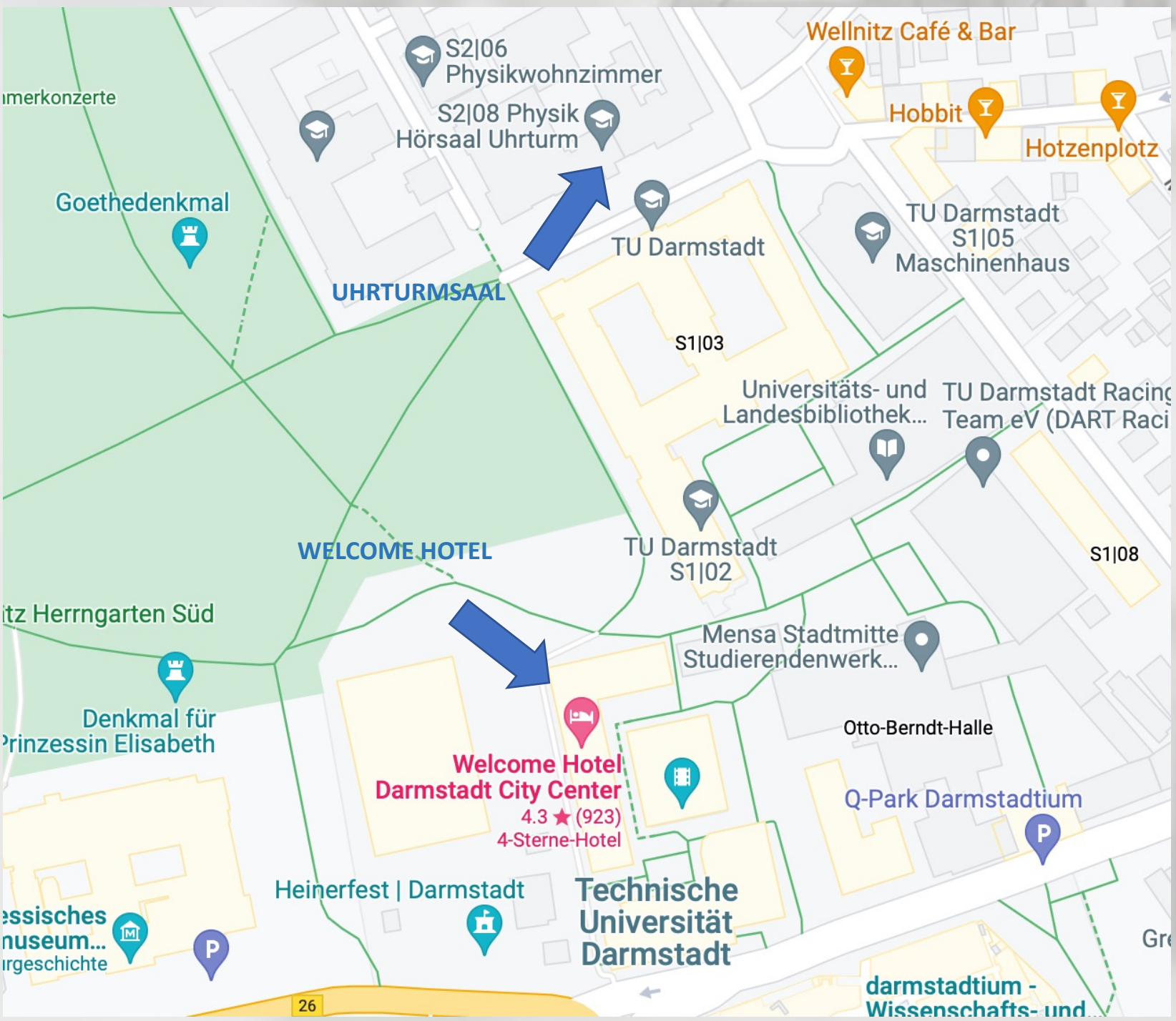
Uhrturmhörsaal

The Conference Venue is the Uhrtumhörsaal

The Uhrturmhösaal is located in S2/08 in the Hochschulstrasse 4. The lecture hall, in which the world's first professor of electrical engineering, Erasmus Kittler, held his lectures, offers the special spatial atmosphere as in 1904 with its elements saved and restored in the original and is therefore very suitable for lecture events.



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