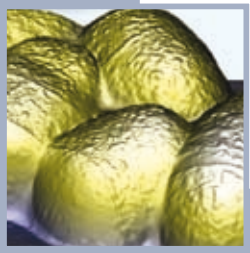
CeBiTec

The Center for Biotechnology at Bielefeld University

CeBiTec



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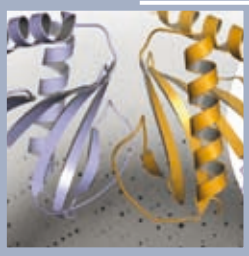

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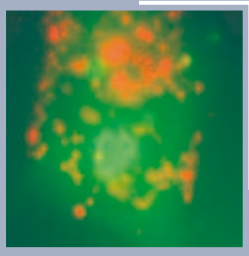

CeBiTec

Februar 2007


CeBiTec

Preface

Within the short space of just a few years, the Center for Biotechnology (CeBiTec) at Bielefeld University has become a major, international research establishment of exceptional quality. It utilizes both the predominant impulse for the University's foundation and a successful and cultivated scientific tradition, this being Interdisciplinarity.

Over the last decades, the life sciences have managed to breakdown the traditional barriers more effectively than any other interdisciplinary fields. This is not only in relation to the barriers between the natural sciences themselves, but also, somewhat, in relation to the barriers that could exist with reference to technological subjects such as informatics – particularly to bioinformatics, the pioneering combination witnessed in Bielefeld. All this currently enables the CeBiTec to realize forward-looking ideas: ideas which bring research further and solve the mysteries which the life sciences pose. Ideas, which when realized, can, in time, be practically applied to the everyday life of all individuals. Here we see the emergence of the scientific basis for the development of new pharmaceuticals, for the optimization of animal feeds in farming or for new technology used in environmental protection such as the application of pollution-eating bacteria, to name but a few.

The CeBiTec has continually expanded and has developed a clear and well-framed structure which, as a result, has enabled optimal interdisciplinary exchange between various fields. Currently, it consists of The Institutes for Bioinformatics, Genome Research and Systems Biology, Biophysics and Nanoscience and the recently established Institute for Biochemistry and Bioengineering. Additionally, there are also the International Graduate School in Bioinformatics and Genome Research and the Bioinfomatics Resource Facility.

This compact organizational structure is now to be complimented by a structure of a physical nature. The necessity for the CeBiTec to have its own laboratory building which is capable of meeting the highest demands of modern research and is at the same time architecturally appealing, has been realized and the new building was officially opened in February 2007. This represents the most extensive building project at Bielefeld University since the construction of the main building more than 30 years ago. The University feels extremely fortunate that this construction project was able to take place under the current adverse climate in public spending. This, perhaps, demonstrates quite clearly how much importance is attached to the research carried out by the CeBiTec, as seen from a political perspective. The University also sees this as a sign of appreciation of our significant efforts in building a profile for seminal scientific fields.

Through the policy relating to the appointment of academics, the interdisciplinary focus of Bielefeld University has been strengthened over the past few years, despite general financial conditions being unusually difficult. The CeBiTec has deliberately exerted a great appeal to ambitious researchers, and will definitely continue to do so in the future. There are no less than 250 members of staff, working under optimal conditions which include the possibility for all to work in close proximity.

At the same time, the CeBiTec has an important role in the promotion of the next generation of young scientists, consistently encouraging their development. The International Graduate School in Bioinformatics and Genome Research offers the ideal conditions for post-doctoral research and provides a starting platform for a successful scientific career. Furthermore, the CeBiTec has also developed innovative new courses of study which attract gifted students from all over the world.

The CeBiTec not only shines in the international world of science. Additionally, it has important cooperation partners in many branches of industry, including multinational companies, with which it realizes high calibre projects and it also advises companies within the Bielefeld area which, for example, operate in a nanoscience context.

I am sure that, in the future, the CeBiTec will initiate important impulses for development in the key areas of the natural sciences and technology, and would like to wish all participating scientists the highest success in their work. May I wish you the utmost pleasure in reading this brochure, which provides an insight into the diversity of research carried out by the CeBiTec.

Prof. Dr. Dieter Timmermann

Rector, Bielefeld University, January 2007

Table of Contents

Center for Biotechnology

**Prof. Dr.
Alfred Pühler**

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The Center for Biotechnology (CeBiTec) at Bielefeld University is dedicated to interdisciplinary research in life sciences. Its mission is to encourage and to support the development of innovative projects crossing discipline boundaries. The close collaboration of scientists from the Faculties of Biology, Chemistry, Physics and from the Faculty of Technology in various research projects is supported by the German Research Foundation (DFG), the Federal Ministry of Education and Research (BMBF), the State Northrhine Westfalia and the European Union.

The interdisciplinary Center for Biotechnology was established by the Senate of Bielefeld University in 1998. During the first years, the scientific members of the CeBiTec were heavily engaged in defining joint research projects. It turned out that the combination of Bioinformatics and Genome Research was of highest importance for the further development of the CeBiTec.

In the year 2000 a grant proposal in the frame of the DFG Initiative 'Bioinformatics' was positively evaluated. The financial support together with a matching fund from Bielefeld University allowed the establishment of two CeBiTec institutes, the Institute for Bioinformatics (inauguration in 2002) and the Institute for Genome Research (inauguration in 2003), which was recently renamed as the Institute for Genome Research and Systems Biology. The detailed structure of the institutes is presented in Figure 1. It is of special importance that both institutes host several junior research groups which use the CeBiTec infrastructure for independent research. It is also worth to mention that the Bielefeld University Bioinformatics Server (BiBiServ) is incorporated into the Institute for Bioinformatics as a technology platform providing more than 30 software tools and various education media. On the other hand, the Institute for Genome Research and Systems Biology is equipped with the Technology Platform Genomics supporting all the high-throughput technologies

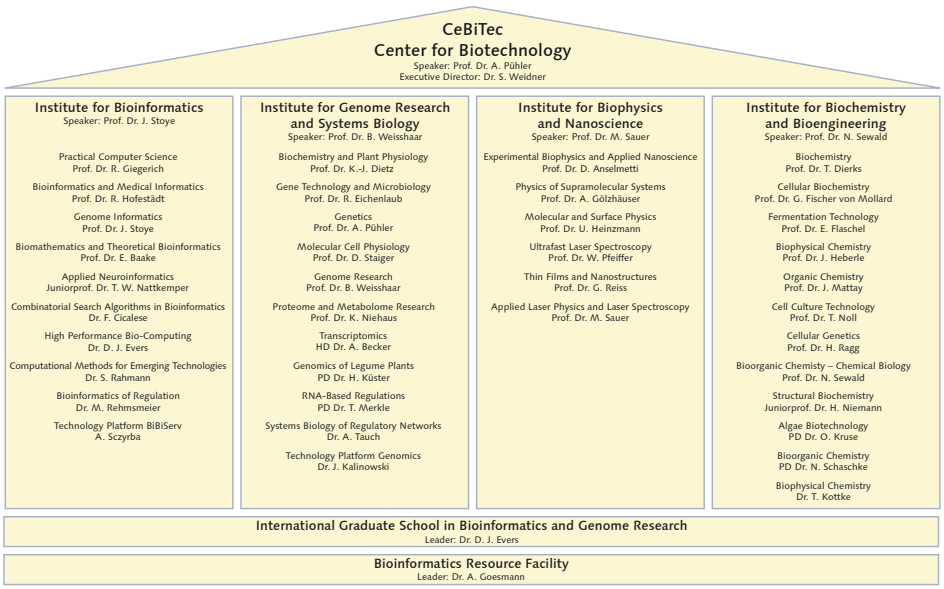

Fig. 1: Curent organization chart of the CeBiTec.

playing a role in genomics, transcriptomics, proteomics and metabolomics. In the year 2000, a further successful project was funded by the German Research Foundation (DFG). This time, the Research Training Group 'Bioinformatics' could be established which finances PhD students for a period of nine years.

The year 2001 turned out to be very successful for the scientific members of the CeBiTec since they were able to acquire several large scale research projects. First of all, the International Graduate School in Bioinformatics and Genome Research financed by the State Northrhine Westfalia, could be established. This Graduate School (see Figure 1) initially planned for five years has been extended. In the meantime nearly 80 PhD students, many of them coming from abroad, have been admitted to the study program. Second, the Competence Network 'Genome Research on Bacteria relevant for Agriculture, Environment and Biotechnology', initially financed for five years by the Federal Ministry of Education and Research (BMBF) has been installed.

Fig. 2: Laying of the cornerstone in October 2004; attendant: A. Pühler (CeBiTec Speaker), U. Günther (BLB Director), D. Timmermann (Rector of Bielefeld University), H.-J. Simm (Chancellor of Bielefeld University), H. Grube (Burgomaster).

Development of CeBiTec

25.09.98	Establishment of the CeBiTec by the Senate of Bielefeld University, adoption of the first Statute
21.12.98	First meeting of the Executive Board, election of Prof. Dr. J. Lehmann as CeBiTec Speaker
14.09.00	Grant from the German Research Foundation (DFG) for the establishment of Institutes for Bioinformatics and Genome Research at Bielefeld University
01.10.00	Grant from the German Research Foundation (DFG) for the establishment of a Research Training Group 'Bioinformatics'
21.06.01	Grant from the Ministry of Education and Research (MSWF) of the State Northrhine Westfalia for the establishment of an International Graduate School in Bioinformatics and Genome Research
15.08.01	Grant from the Federal Ministry of Education and Research (BMBF) for the Competence Network 'Genome Research on Bacteria relevant for Agriculture, Environment and Biotechnology'. In June 2006 the project was extended for further three years.
03.12.01	Grant from the German Research Foundation (DFG) for the establishment of the Collaborative Research Center SFB 613 'Physics of Single Molecule Processes and Molecular Recognition in Organic Systems'
05.12.02	Inauguration of the Institute for Bioinformatics
13.02.03	Inauguration of the Institute for Genome Research
27.02.04	General meeting of the CeBiTec and election of the current Executive Board, election of Prof. Dr. A. Pühler as Speaker of the CeBiTec Executive Board
19.10.04	Laying of the cornerstone for the CeBiTec laboratory building at Bielefeld University
22.04.04	Inauguration of the Bielefeld Institute for Biophysics and Nanoscience (BINAS)
20.10.05	Topping-out ceremony of the new CeBiTec building
18.11.05	Constitutive meeting of the Scientific Advisory Board of the CeBiTec
03.03.06	General meeting of the CeBiTec and election of the current Executive Board, affirmation of Prof. Dr. A. Pühler as Speaker of the CeBiTec Executive Board
30.01.07	Inauguration of the Institute for Biochemistry and Bioengineering (BioChemTech)

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Within this network more than 20 groups from universities, research institutes and industry collaborate in the field of bacterial genome research. Because of the very successful work and collaboration of the Competence Network the funding has been extended for further three years. Combined with this network a Competence Center dedicated to post-genomics was established at the CeBiTec. Finally, at the end of the year 2001 the German Research Foundation (DFG) installed the Collaborative Research Center SFB 613 entitled 'Physics of Single Molecule Processes and Molecular Recognition in Organic Systems'. This was a further important step for the CeBiTec since scientists of the Faculty of Physics got in closer contact with the CeBiTec and discussed the possibility of establishing a third institute. The institute termed Bielefeld Institute for Biophysics and Nanoscience (BINAS), was finally inaugurated in the year 2004.

The highlight of the year 2004 was without doubt the beginning of the construction of the CeBiTec laboratory building. The laying of the cornerstone took place in October 2004 (see Figure 2) followed by the topping-out ceremony in October 2005. Furthermore, the Advisory Board consisting of six distinguished scientists from academia and industry was formed and met for the first time in November 2005 (Figure 3).

At the beginning of the year 2006 the current Executive Board was elected in a general meeting. The members of this board are shown in Figure 4. In June 2006 an international symposium on 'Molecular Systems Biology', organized by the CeBiTec has been carried out at the Center for interdisciplinary Research of Bielefeld University. This workshop assembled leading scientists from the field of molecular biology, mathematics, bioinformatics, chemistry and physics with the aim to foster the interdisciplinary collaboration and to introduce and to integrate Bielefeld University into the International Systems Biology community. By the way, in July 2007 a second CeBiTec symposium on 'The Future of Genome Research in the Light of Ultrafast Sequencing Technologies' will take place. It is dedicated to the delineation of concepts in the field of ultrafast sequencing methods, and to the requirements on bioinformatics concerning the analysis of the emerging huge data sets.

The successful development of the CeBiTec continues with the establishment of a fourth institute, the Institute for Biochemistry and Bioengineering (BioChemTech).

Fig. 3: The Scientific Advisory Board of the CeBiTec; from left to right: Prof. Dr. M. Vingron, Dr. R. Apweiler, Dr. K. Huthmacher, Prof. Dr. R. Amann, Dr. E. Sailer.

Fig. 4: The Executive Board of the CeBiTec; from left to right: Prof. Dr. A. Gölzhäuser, J. Krüger, Prof. Dr. M. Sauer, Dr. S. Rahmann, Prof. Dr. B. Weisshaar, Prof. Dr. A. Pühler, Dr. J. Kalinowski and J. Baumbach.

Its inauguration took place in January 2007. With this institute adding biochemistry and bioengineering the research portfolio of the CeBiTec is completed. Looking to the future, the next important step in the development of the CeBiTec will be the move into the laboratory building which will happen in the first half of 2007. The laboratory building will house the Chair of Genome Research of Bernd Weisshaar as well as the Technology Platform Genomics. In addition several junior groups and the staff of larger research projects will find laboratory space in the new building. The most recent exterior view of the CeBiTec building is shown in Figure 5.

Evidently, the development of the CeBiTec research center constitutes a success story. In the meantime, it represents a location where research groups from four different faculties collaborate intensively in the field of future oriented life sciences. It is expected that the existing structure of the CeBiTec will be able to take up new research questions and to react on changing research developments.

Bielefeld, February 1st, 2007

Prof. Dr. Alfred Pühler

Fig. 5: The most recent exterior view of the CeBiTec laboratory building.

CeBiTec – Executive Board

Prof. Dr. A. Gölzhäuser
Representative of professoriate

Prof. Dr. A. Pühler
Speaker of the Executive Board and representative of professoriate

Prof. Dr. M. Sauer
Speaker of the Bielefeld Institute for Biophysics and Nanoscience

Prof. Dr. J. Stoye
Speaker of the Institute for Bioinformtics

Prof. Dr. B. Weisshaar
Speaker of the Institute for Genome Research and Systems Biology

Dr. J. Kalinowski
Representative of scientific staff members

Dr. S. Rahmann
Representative of scientific staff members

J. Baumbach
Representative of PhD students and back staff

J. Krüger
Representative of additional staff members

CeBiTec – Scientific Advisory Board

Prof. Dr. R. Amann
MPI for Marine Microbiology, Bremen

Dr. R. Apweiler
EMBL Outstation, European Bioinformatics Institute, Hinxton, UK

Prof. Dr. M. Grunze
Ruprecht-Karls-Universität, Heidelberg

Dr. K. Huthmacher
Degussa AG, Hanau

Dr. E. Sailer
Miele & Cie. KG, Gütersloh

Prof. Dr. M. Vingron
MPI for Molecular Genetics, Berlin

Institute for Bioinformatics

Prof. Dr.
Jens Stoye

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Modern molecular biology requires mathematical models and efficient algorithms to interpret the mass of observations generated by current experimental techniques. This necessity has given birth to the new discipline of bioinformatics.

Bioinformatics can roughly be split in two branches: **Algorithmic Bioinformatics** is concerned with new methods of data analysis, resulting in new or better models, algorithms and tools. This branch needs input from biology, but is mainly a computer science activity with its typical cycle of algorithm development, implementation and evaluation.

Applied Bioinformatics is the actual interpretation of biological data with the tools developed in the algorithmic branch of the field. This requires close cooperation between biologists and bioinformaticians, in particular when novel experimental techniques or novel tools are involved.

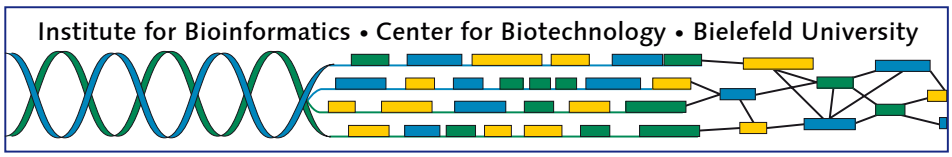
The Institute for Bioinformatics at Bielefeld University is engaged in both kinds of activities. It was founded in 2002 as a consequence of the successful application of Bielefeld University in the DFG Initiative in Bioinformatics. It was incorporated into the Center for Biotechnology (CeBiTec) after its new constitution in 2004.

The institute is a forum for communication and joint research in Bioinformatics and Biomathematics at Bielefeld University. The main tasks of the institute are the coordination of interdisciplinary research projects, the organization of workshops and seminars, and the presentation of the activities and results of the involved research groups. One of the largest activities was the organization of the German Conference on Bioinformatics, GCB 2004, with about 280 participants, 28 scientific presentations, and 60 posters.

As of spring 2007, the Institute for Bioinformatics hosts four senior research groups, five junior research groups and one technology platform, the Bielefeld University Bioinformatics Server (BiBiServ), that provides web access to bioinformatics tools and educational material developed in Bielefeld.

Research projects at the Institut for Bioinformatics can roughly be grouped into three main areas: biological sequence analysis, comparative genomics, and bioinformatics for systems biology.

In the area of **sequence analysis**, methods for fast sequence database search, genome assembly including the development of a hybrid assembler for traditional and high-throughput sequencing data, gene prediction, identification of regulatory binding sites, and the analysis of environmental samples are being developed. Other ma-



jor activities are in computational RNomics like RNA secondary strucure analysis or target prediction of microRNAs. At a more abstract level, index structures for large-scale sequence comparison are being studied, general search algorithms in bioinformatics, and a new algebraic approach to dynamic programming has been developed.

Projects in **comparative genomics** include the development of methods for large-scale differential comparative genome analysis, for cross-species prediction of full-length cDNAs, and algorithms for genome rearrangements and gene cluster detection.

In the area of **bioinformatics for systems biology**, problems that arise during the integration of information from different data sources are addressed, models of regulatory and metabolic networks are developed, and simulations are performed. Also, questions arising from technological developments for systems biology are being addressed: microarray design, analysis of mass spectra, image analysis, data and text mining.

Outside the core areas listed above, members of the institue are also active in fields closely related to bioinformatics, including medical informatics, biomathematics and population genetics.

Contributing Units

Practical Computer Science
Prof. Dr. Robert Giegerich

Bioinformatics and Medical Informatics
Prof. Dr. Ralf Hofestädt

Genome Informatics
Prof. Dr. Jens Stoye

Biomathematics and Theoretical Bioinformatics
Prof. Dr. Ellen Baake

Applied Neuroinformatics
Juniorprof. Dr. Ing. Tim W. Nattkemper

Combinatorial Search Algorithms in Bioinformatics
Dr. Ferdinando Cicalese

High Performance Bio-Computing
Dr. Dirk J. Evers

Computational Methods for Emerging Technologies (COMET)
Dr. Sven Rahmann

Bioinformatics of Regulation
Dr. Marc Rehmsmeier

Technology Platform Bielefeld University Bioinformatics Server (BiBiServ)
Alexander Sczyrba

Robert Giegerich

1981: PhD, TU Munich, Germany
1981-1984: Postdoctoral position, TU Munich, Germany
1985-1986: Postdoctoral position, University Dortmund, Germany
1987-1989: Professor for Programming Languages and Compilers, University Dortmund, Germany
Since 1989: Professor for Practical Computer Science, Bielefeld University, Germany

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Selected publications

Beckstette, M. *et al.*: 2006. **Fast index based algorithms and software for matching position specific scoring matrices.** BMC Bioinformatics, 7: 389

Steffen, P. and Giegerich, R.: 2006. **Table design in dynamic programming.** Information and Computation, 204: 1325-1345

Reeder, J. *et al.*: 2005. **Effective ambiguity checking in biosequence analysis.** BMC Bioinformatics, 6: 153

Reeder, J. and Giegerich, R.: 2005. **Consensus shapes: An alternative to the Sankoff algorithm for RNA consensus structure prediction.** Bioinformatics, 21: 3516-3623

Choudhuri, J. *et al.*: 2004. **Genalyzer: Interactive visualization of sequence similarities between entire genomes.** Bioinformatics, 20: 1964-1965

Giegerich, R. *et al.*: 2004. **A discipline of dynamic programming over sequence data.** Science of Computer Programming, 51: 215-263

Giegerich, R. *et al.*: 2004. **Abstract Shapes of RNA.** Nucleic Acids Res., 32: 4843-4851

Large scale sequence analysis and computational RNA biology

Previous and Current Research

Programming languages and compilers were the original field of work when the group was first established. Although the research focus has shifted considerably since, the group still holds an interest in this field and pursues active research. The use of declarative (functional) programming languages is propagated in computer science education, as well as in program development for bioinformatics applications. A long term goal here is the realization of a declarative language for dynamic programming, which is of tantamount importance in biosequence analysis.

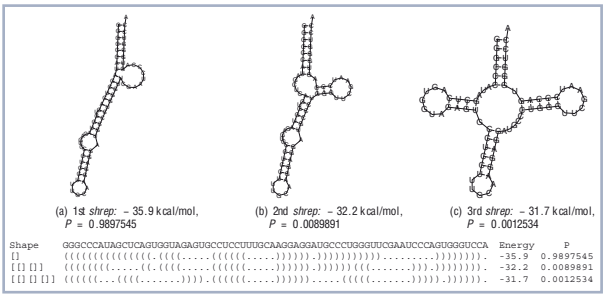
For *large scale analysis*, a variety of tools has been developed, such as REPuter (for fast computation of degenerative repeats in complete genomes) and GENlight (an interactive system for high-throughput sequence analysis and comparative genomics), e2g (matching ESTs to genomic sequence), and MGA (multiple genome alignment). We have made several contributions to make suffix trees and suffix arrays practical as index data structures for sequence analysis.

For *RNA structure analysis* we provide tools that define the state of the art in several respects, such as RNAforester (structure comparison and multiple structure alignment), pknotsRG (folding structures with pseudoknots), and RNAhybrid (miRNA target prediction). We introduced the method of abstract shape analysis and are exploring its manifold consequences. Recent tools based on this approach are RNAshapes (shape analysis) and RNAcast (consensus structure prediction).

In *programming methodology*, we have developed the discipline of Algebraic Dynamic Programming (ADP). It raises dynamic programming over sequence data to a higher level of abstraction, considerably enhancing programming productivity, program reliability and reusability. Several of the aforementioned tools were implemented with this technique.

Future Projects and Aims

Recent years have brought surprising discoveries and tremendous interest in the multi-facet functions of RNA in gene regulation. Computational RNA biology so far has dealt mostly with one molecule at a time. As research on the functional role of RNA is moving towards the whole genome scale, our tools must be sharpened considerably. Our goal is to bring together techniques of large scale sequence analysis with improved techniques for RNA structure prediction, comparison and motif detection.



The program RNAshapes computes representative near-optimal secondary structures of an RNA-molecule.

Ralf Hofestädt

1990: PhD, University of Bonn, Germany
1995: Habilitation, University Koblenz-Landau, Germany
Since 1996: Professor for Applied Computer Science, University of Magdeburg, Germany
Since 2001: Professor for Bioinformatics and Medical Informatics, Bielefeld University, Germany

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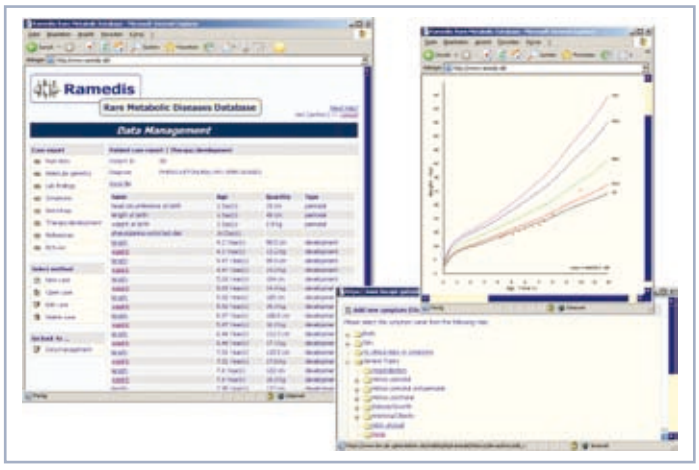
Biomedical information systems and data integration

Previous and Current Research

The RAMEDIS system is a platform-independent, web-based information system for rare diseases based on individual case reports. It was developed in close cooperation with clinical partners and collects information on rare metabolic diseases in extensive detail (e.g. symptoms, laboratory findings, therapy and genetic data). This combination of clinical and genetic data enables the analysis of genotype-phenotype correlations. By using largely standardized medical terms and conditions, the contents of the database are easy to compare and analyze. In addition, a convenient graphical user interface is provided by every common web browser. RAMEDIS supports an extendable number of different genetic diseases and enables cooperative studies. Furthermore, use of RAMEDIS should lead to advances in epidemiology, integration of molecular and clinical data, and generation of rules for therapeutic intervention and identification of new diseases.

Future Projects and Aims

Recent technological advances have greatly increased the capability to investigate complex molecular interactions that occur in the onset of disease in order to identify genetic alterations and to screen new drugs. Target identification is essential to screen and synthesize new bioactive molecules that can interact with them. Cardiovascular diseases (CAD) are one of the major groups of multifactorial diseases and are one the main causes of mortality and morbidity in most developed countries.
The aim of this project is to improve the target selection/validation process and optimize drug design for cardiovascular diseases. We have focused on atherosclerosis. In recent years research in this field has acquired a multidisciplinary style, due to the increase in knowledge about cellular and molecular mechanisms involved in the onset and progress of atherosclerosis. Cardiovascular diseases provide a relevant domain for the development of a new multidisciplinary approach to target selection and validation. In the Cardioworkbench project groups with complementary expertise are involved, specifically, computer scientists, clinicians, molecular/cellular biologists and pharmacologists will combine their expertise.



Screenshots of a sample case report in RAMEDIS with presentation of main data and growth parameters. The lower right screenshot shows a symptom tree for entering a new symptom to the case report and the upper right screenshot shows a graphical visualization of the growth parameter length.

Selected publications

Chen, M. and Hofestädt, R. 2006. **A medical bioinformatics approach for metabolic disorders: Biomedical data prediction, modeling, and systematic analysis.** Journal of Biomedical Informatics, 39: 147-159

Töpel, T. *et al*.: 2006. **RAMEDIS, the rare metabolic diseases database.** Applied Bioinformatics, 5: 115-118

Hofestädt, R. and Töpel, T.: **Medical Bioinformatics: Detecting molecular diseases with case-based reasoning.** In: Bioinformatics using Computational Intelligence Paradigms, U. Seiffert (ed.). Springer-Verlag, 2005: 1-24

Kolchanov, N., Hofestädt R. and Milanesi L. (eds.): **Bioinformatics of genome regulation and structure II.** Springer, New York, 2006

Collado-Vides, J. and Hofestädt R. (eds.): **Gene regulation and metabolism - post-genomic computational approaches.** Cambridge, MA: MIT Press, 2002

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1997: PhD, Bielefeld University, Germany
1997-1998: Postdoctoral position, UC Davis, U.S.A.
1998-2001: Postdoctoral position, DKFZ Heidelberg, Germany
2001-2002: Group leader, MPI for Molecular Genetics, Berlin, Germany
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Selected publications

Didier, D. *et al*.: Character sets of strings. J. Discr. Alg., to appear

Bergeron, A. *et al*.: 2006. On sorting by translocations. J. Comp. Biol. 13: 567-578

Rasmussen, K. *et al*.: 2006. Efficient q-gram filters for finding all epsilon-matches over a given length. J. Comp. Biol. 13: 296-308

Gusfield, D. and Stoye, J. 2004. Linear time algorithms for finding and representing all the tandem repeats in a string. J. Comput. Syst. Sci. 69: 525-546

Giegerich, R. *et al*.: 2003. Efficient implementation of lazy suffix trees. Softw. Pract. Exper. 33: 1035-1049

Genome structure and dynamics

Previous and Current Research

Comparative Genomics is a powerful paradigm for the analysis of genomic data, applied in several contexts, from functional annotation of genes to phylogenomics and comparison of whole genomes. The dramatically increasing amount of available data requires an important research effort in the development of comparative models, biologically sound and mathematically well understood, and of efficient algorithms and software that can handle large data sets.

To achieve these goals, various lines of research are conducted in the Genome Informatics group. In sequence analysis, we develop index-based analysis methods for large-scale sequence comparison, pattern search, and pattern discovery. Other projects consider genomes at the level of gene orders. Here, we are interested in developing mathematically sound models of gene clusters, and efficient algorithms for their detection. We are also working on models and algorithms for genomic rearrangement. The Double-Cut-and-Join (DCJ) Operation that has been recently suggested by Yancopoulos *et al*. (2005) allows to model all the classical genome rearrangement operations such as inversions, translocations, fissions, fusions, and transpositions. While it is known that the different operations are unequally likely and hence can not simply be replaced by the DCJ operation, it has been shown that based on this unifying concept the formal treatment of the other operations can be simplified considerably. In this sense the DCJ operation can be seen as an important tool with the potential to go even beyond the classical questions, addressing rearrangement problems that involve either gene duplications or missing information about the actual order of genes in a genome.

Future Projects and Aims

Historically, genomic sequence analysis and genome rearrangement studies have been performed at different levels of granularity: While in sequence analysis the DNA bases are the basic entites, in rearrangement studies the order of genes or other unique markers in the evolving genome is studied. Unifying both pictures into one mathematical model is one of our goals. Moreover, we believe that the mathematical theory of genome rearrangements can be considerably simplified. With our studies of the DCJ operation and its connection to the inversion and translocation models we have done first steps in this direction, but we believe that much more is possible.

The tryptophan biosynthesis gene cluster, detected in seven *Actinobacteria* and in *L. lactis* with the tool Gecko developed in the Genome Informatics group, http://bibiserv.techfak.uni-bielefeld.de/gecko/. Each arrow represents a gene, where the same color denotes genes from the same family.

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2002: Juniorprofessor for Applied Neuroinformatics, Bielefeld University, Germany

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Multivariate bioimage analysis

Previous and Current Research

Nowadays we observe a growing number of computer science applications from the field of computational intelligence in the domains of bioinformatics and medical data analysis. The applied algorithms are rooted in the fields of pattern recognition, artificial neural networks (ANN) or machine learning (ML). ANN and ML algorithms can learn non-linear mappings from even noisy labelled data sets and have the potential to analyze complex data structures in high-dimensional spaces. The research of the Applied Neuroinformatics group aims at exploring these promising potentials for the analysis of data from biology and biomedicine as well as clinical data.

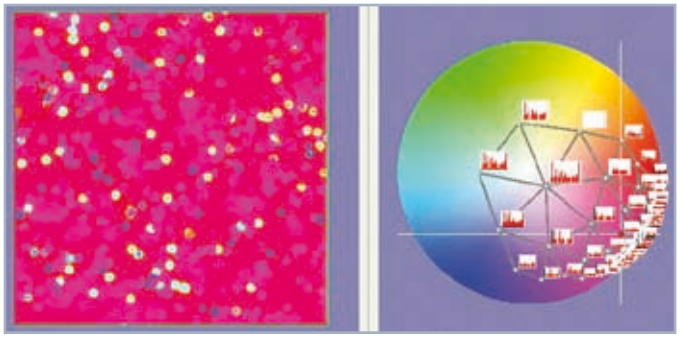
One focus of our attention is the development of approaches that support the exploratory data analysis by non-computer-expert users. This can be achieved for instance by developing software tools which can be used more intuitively based on the primary expertise of the biologist. Using these software tools the user can explore data in data driven visualizations which have been tuned based on expert knowledge. Other works apply novel dimension reduction and clustering techniques to find hidden regularities in biomedical data.

Future Projects and Aims

The application of learning algorithms in such frameworks demands further research, since an application of these algorithms in a real world study is not straightforward. This is mainly caused by missing prerequisites. Some of the most frequent problems are for example unbalanced data sets or missing background knowledge like gold standards. All our research projects include the development of solutions to these problems. One major prerequisite for solving these problems has always been the close collaboration with our partners from biology and medicine.

Cooperations

The group cooperates with other university departments in Bielefeld (like the Neural Networks Group, the Theoretical Physics Group, the Faculty of Biology and the Faculty of Public Health), local medical service centers (like City Hospital, the Institute of Neuropathology and the Gilead Hospital) as well as international partners (like for instance the Institute of Cancer Research (UK), Unilog IT Servises (Switzerland), the Universidade Federal do Caera (Brazil) and the Florida State University (U.S.A.)). The group currently consists of nine PhD students and eight undergraduates.



On the right: Using new approaches for clustering and dimensional reduction, like the hyperbolic self-organizing map (HSOM), the n-dimensional signal patterns of single pixels are mapped onto a lower dimensional grid. On the left: By mapping two dimensional scales (for instance hue and saturation) on the low dimensional grid, the image space can be dynamically visualized using pseudocolors.

Selected publications

Wei, N. *et al.*: 2006. ***In situ* dark field microscopy for on-line monitoring of yeast cultures.** Biotechnology Letters, in press

Nattkemper, T.W. *et al.*: 2005. **Evaluation of radiological features for breast tumour classification in clinical screening with machine learning methods.** Artificial Intelligence in Medicine, 34: 129-139

Saalbach, A. *et al.*: 2005. **Image fusion based on topographic mappings using the hyperbolic space.** Information Visualization, 4: 266-275

Twellmann, T. *et al.*: 2005. **An adaptive tissue characterization network for model-free visualization of dynamic contrast enhanced magnetic resonance image data.** IEEE Transaction on Medical Imaging, 24: 1256-1266

Nattkemper, T.W.: 2004. **Multivariate image analysis in biomedicine: a methodological review.** Journal of Biomedical Informatics, 37: 380-391

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Selected publications

Cicalese, F. and Deppe, C.: 2007. **Perfect minimally adaptive q-ary search with unreliable tests.** J. Stat. Plan. Inference, 137: 162-175

Cicalese, F. and Laber, E.: 2006. **On the competitive ratio of evaluating priced functions.** In Proc. of SODA, 944-953

Cicalese, F. *et al.*: 2006. **A note on approximation of uniform distributions from variable-to-fixed length codes.** IEEE Transactions on Information Theory, 52: 3772-3777

Cicalese, F. *et al.*: 2006. **Overlaps help: improved bounds for group testing with interval queries.** Discrete Applied Mathematics, 155: 288-299

Cicalese, F. *et al.*: 2005. **Optimal group testing algorithms with interval queries and their application to splice site detection.** Int. Journ. Bioinf. Res. And Appl. (IJBRA), 1: 363-388

Cicalese, F. and Laber, E.: 2005. **A new strategy for querying priced information.** In Proc. of STOC, 674-683

Cicalese, F. and Laber, E.: 2005. **An optimal algorithm for querying priced information: monotone Boolean functions and game trees.** In Proc. of ESA, 664-676

Combinatorics in computational biology

Previous and Current Research

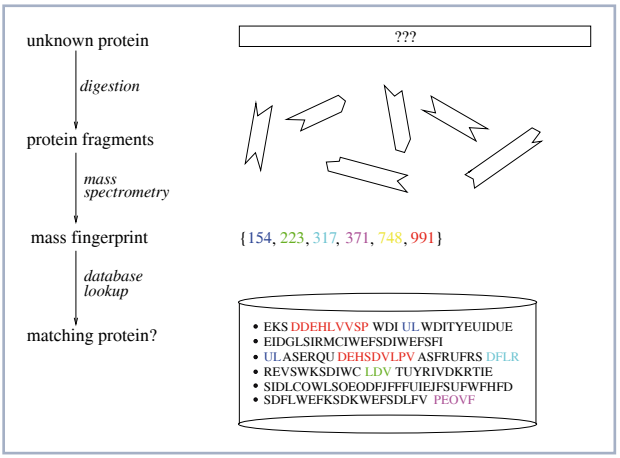
The main research activity of the group is the design and analysis of efficient algorithms for the solution of combinatorial search problems arising in the field of Bioinformatics. The group concentrates on the solution of concrete problems in genetics and proteomics but also on the new theoretical issues that such problems raise in the field of combinatorial search theory, specifically combinatorial group testing. Group testing is a basic search paradigm which occurs in a variety of situations such as quality control in product testing, multiple access communication, medical diagnosis, pattern classification, machine learning, the design of scientific experiments, data compression, and not least computational molecular biology, among others. Presently, the group is studying the employment of the group testing machinery to tackle the following problems in molecular biology: splice site detection, MS-protein mixtures identification, q-gram identification. On a more theoretical level, we investigate efficient procedures for accessing data bases including complex data objects.

Future Projects and Aims

Both for theoretical and practical purposes, a deeper understanding of the combinatorial complexity of the problem of protein identification is needed. A new line of research that we aim to follow is the analysis of this problem as a particular instance of the characterization and enumeration of unions of hitting sets of a hypergraph. This is part of a new international project the group is organizing together with researchers from the Chalmers University (Sweden) and the University of Tennessee (U.S.A.).

Cooperations

In-house collaborations have been established with several groups, among them the Research Group Combinatorics and Information Theory of Prof. Rudolf Ahlswede at the Faculty of Mathematics, and the other junior research groups at the Genome Informatics research group. Outside Bielefeld University, we collaborate with the Departments of Computer Science at Chalmers University (Sweden), at Pontifica Universidade do Rio de Janeiro (Brasil), at University of Salerno (Italy), at University of Bergen (Norway), as well as with the Department of Mathematics at University of Florence (Italy).



Protein mixtures identification with PMF.

Dirk J. Evers

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Since 2003: Leader of the Junior Research Group High Performance Bio-Computing, Bielefeld University, Germany
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Hybrid *de novo* genome assembly

Previous and Current Research

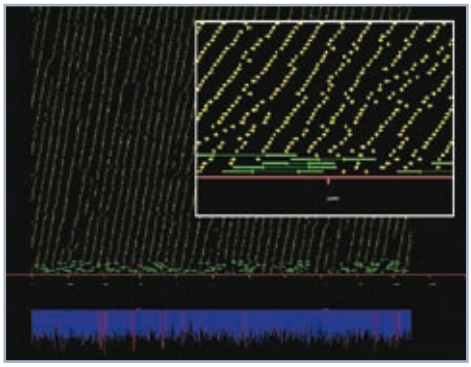
The life sciences have long passed the point where comprehensive analysis of typical data sets is still possible on a single industry standard personal computer. While the speedup of computers is continuing to rise exponentially according to Moore's law, so is the volume of data, but at a higher rate! We are looking for ways to computationally analyze data sets acquired by high-throughput technology on affordable compute clusters, as found in life science research institutions all over the world.

Among other things, we are interested in ultrafast DNA sequencing technology and its algorithmic implications. Currently, new sequencing methods by companies such as 454, Solexa, Agencourt Personal Genomics, and Helicos are reaching the market, with the promise of significant improvements in overall cost, speed, and quantity. On the downside are considerably shorter average read lengths, complex error topologies, and as-yet unpaired reads. The forge/G genome assembler under development at the CeBiTec and the DOE Joint Genome Institute is capable of combining conventional paired-end Sanger reads with single short reads from a 454 sequencing system in one hybrid assembly. Overlap statistics, alignment, and consensus calculations need to take into account mixed populations of different read lengths and error characteristics. The assembly process is divided into five phases: preprocessing (clipping), hash-generation/overlap detection, two-pass graph generation, and linearization. All phases of forge/G are implemented as parallel algorithms targeted toward optimal performance on a typical cluster of industry standard personal computers. The resulting system is flexible and has been used successfully on bacterial and fungal genomes, conventional whole-genome shotgun projects, pooled clones, meta-genomic samples and both modern and ancient DNA.

Future Projects and Aims

Our aim is to extend the assembler to utilize ultra-short reads of 25 bases such as the sequencing systems developed by Solexa, Agencourt Personal Genomics, and Helicos provide. For this to succeed, new highly efficient algorithms for overlap detection need to be developed.

Hardware accelerated algorithms are one answer to tackle the data flood. We plan to adapt parts of the forge/G assembler in order to work with FPGA (field programmable gate array) hardware. Another project in planning is the adaptation of the algebraic dynamic programming (ADP) compiler, developed at the Practical Computer Science group of Prof. Robert Giegerich to produce FPGA code. This would enable computer scientists to produce highly efficient parallel code for dynamic programming problems that abound in bioinformatics.



Visualization of part of a forge/G assembly of Prochlorococcus: Conventional sanger sequenced reads with 2x coverage (green) together with short reads from a 454 run (yellow) and depth of coverage (blue).

Selected publications

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Evers, E. and Giegerich, R.: 1999. **RNA movies: Visualizing RNA secondary structure spaces.** Bioinformatics, 15: 32-37

Stoye, J. *et al.*: 1998. **Rose: Generating sequence families.** Bioinformatics, 14: 157-163

Stoye, J. *et al.*: 1997. **Generating benchmarks for multiple sequence alignments and phylogenetic reconstructions.** Proc. Int. Conf. Intell. Syst. Mol. Biol., 5: 303-306

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Selected publications

Baumbach, J. *et al.*: 2006. **CoryneRegNet: An ontology-based data warehouse of corynebacterial transcription factors and regulatory networks.** BMC Genomics, 7: 24

de Carvalho Jr., S.A. and Rahmann, S.: 2006. **Improving the layout of oligonucleotide microarrays: Pivot Partitioning.** Proceedings of the 6th Workshop of Algorithms in Bioinformatics (WABI), LNBI 4175: 321-332. Springer-Verlag

Klau, G. W. *et al.*: 2006. **Integer linear programming approaches for non-unique probe selection.** Discrete Applied Mathematics. doi:10.1016/j.dam.2005.09.021

Rahmann, S.: 2003. **Fast large scale oligonucleotide selection using the longest common factor approach.** J. Bioinform. Comput. Biol., 1: 343-361

Rahmann, S. *et al.*: 2003. **On the power of profiles for transcription factor binding site detection.** Statistical Applications in Genetics and Molecular Biology, 2: Article 7

Emerging technologies and systems biology

Previous and Current Research

Our research interests cover a broad range from the theoretical to the applied end of algorithmic and statistical computational biology.

On the theoretical side, we are interested in statistical and combinatorial questions about strings and sequences, such as the number of distinct subsequences contained in a given sequence. Answers to such problems have applications to oligonucleotide microarray design and large-scale DNA sequencing.

A major focus of the group is modeling transcriptional regulation. This consists, for example, of modeling and efficiently discovering binding site motifs, and of investigating the possibilities and limitations of reverse engineering regulatory networks. As a general infrastructure for further algorithm engineering, we have developed the data warehouse CoryneRegNet, a comprehensive information resource on corynebacterial transcriptional regulation that also includes data on *E. coli* K-12 from RegulonDB. To identify new DNA binding motifs of transcription factors, we use comparative genomics approaches and algorithmic stochastics.

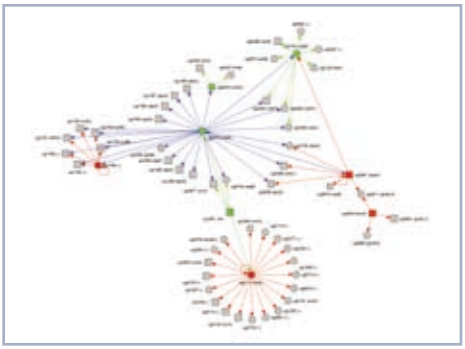
Group members also have considerable experience in microarray design. In one of our projects we have developed the LoligoD software for large-scale oligonucleotide design. Another project aims at optimizing the layout of the probes on the chip for the best possible quality. A third project models and predicts cross-hybridization of short and long oligonucleotides and will help to increase data quality in transcriptomics, which is essential when we integrate microarray data into whole systems biology projects.

In computational proteomics, we have developed statistical models for peptide fragment masses after enzymatic cleavage. These are useful tools when proteins from a sample have to be identified by their mass fingerprint; our models improve the classification accuracy for difficult cases.

Future Projects and Aims

The next goal is to extend our data warehouse infrastructure, so we can provide a universal framework that can be adapted to study gene regulation in any prokaryotic organism. CoryneRegNet itself will be enhanced by microarray experiments and protein-protein interactions, providing a more detailed picture of regulation.

In the long term, new large-scale sequencing technologies pose new interesting combinatorial and algorithmic problems. On the practical side, we are interested in applying them to discover epigenetic patterns.



A small part of the transcriptional regulation network of *Corynebacterium glutamicum*, as represented by CoryneRegNet, a database of regulatory relationships in *Corynebacteria* developed in the COMET group.

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1996-2001: PhD studies, Theoretical Bioinformatics, DKFZ, Heidelberg, Germany
2002-2004: Mentor at the International NRW Graduate School in Bioinformatics and Genome Research, CeBiTec, Bielefeld University, Germany
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Bioinformatics of Regulation

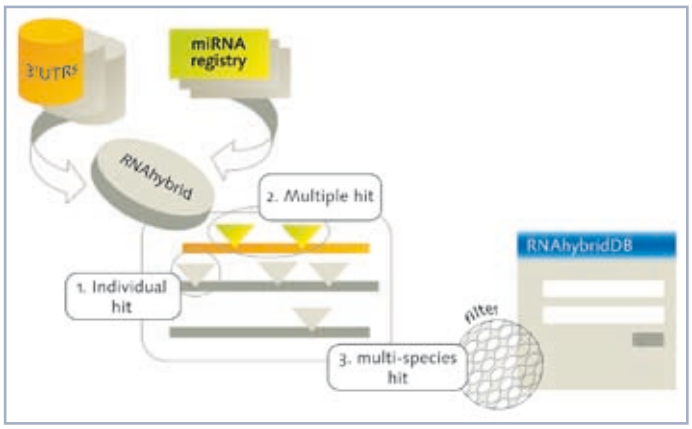
Previous and Current Research

Our main interests are RNA Bioinformatics and Regulatory DNA Elements. In RNA Bioinformatics, the focus is on the analysis of microRNAs (miRNAs) and their targets. We have developed a program for miRNA target prediction, RNAhybrid (Rehmsmeier *et al*. 2004), which considers binding energies of miRNA/target duplexes, statistical significance of individual and multiple binding sites, and evolutionary conservation of miRNA/target relationships (see Figure). Further contributions are in the field of RNA secondary structure analysis (Giegerich *et al*. 2004, Voß *et al*. 2006). This theoretical work has been achieved in collaboration with Robert Giegerich at Bielefeld University.

The focus in the area of Regulatory DNA Elements is the analysis of Polycomb/Trithorax Response Elements (PRE/TREs or PREs for short). PREs are epigenetic switch elements that maintain previously determined transcription states of their associated genes over many generations of cell divisions, thus establishing a memory of transcriptional history. An important result of our work is the prediction of PREs in *Drosophila melanogaster* (Ringrose *et al*. 2003). In these studies we are cooperating closely with experimental groups (Renato Paro, ZMBH Heidelberg, Germany; Leonie Ringrose, IMBA Vienna, Austria).

Future Projects and Aims

We are currently validating miRNA target predictions with luciferase reporter assays, and we are developing a database of predicted miRNA targets. We are also collaborating with internal and external groups, both in the further development of target prediction (Thomas Merkle, Bielefeld University, Germany; Anton Enright, Wellcome Trust Sanger Institute, Cambridge, UK) and in the experimental analysis of predicted miRNA/target relationships (Thomas Merkle; Javier Martinez, IMBA Vienna, Austria; Gerhard Schratt, Heidelberg University, Germany). The PRE study we are extending to an evolutionary analysis in several *Drosophila* species and to the prediction of developmental and other enhancers in *Drosophila*.



Workflow of the RNAhybrid miRNA target prediction approach.

Selected publications

Voss, B. *et al*.: 2006. **Complete probabilistic analysis of RNA shapes**. BMC Biol., 4: 5

Giegerich, R. *et al*.: 2004. **Abstract shapes of RNA**. Nucleic Acids Res., 32: 4843-4851

Rehmsmeier, M. *et al*.: 2004. **Fast and effective prediction of microRNA/target duplexes**. RNA, 10: 1507-1517

Ringrose, L. *et al*.: 2003. **Genome-wide prediction of Polycomb/Trithorax Response Elements in *Drosophila melanogaster***. Dev. Cell, 5: 759-771

Alexander Sczyrba

1998: Diploma in Computer Science in the Natural Sciences, Bielefeld University, Germany
1999-2000: Guest Investigator at The Rockefeller University, New York, U.S.A.
2000-2002: Staff member at the Research Group Practical Computer Science, Bielefeld University, Germany
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Selected publications

Seibel, P.N. *et al.*: 2006. **XML schemas for common bioinformatic data types and their application in workflow systems.** BMC Bioinformatics, 7: 490

Sczyrba, A. *et al.*: 2005. **XenDB: Full length cDNA prediction and cross species mapping in *Xenopus laevis*.** BMC Genomics, *6:* 123

Krüger, J. *et al.*: 2004. **e2g: an interactive web-based server for efficiently mapping large EST and cDNA sets to genomic sequences.** Nucleic Acids Res., 32: W301-304

Sczyrba, A. *et al.*: 2004. **Identification of 10,500 *Xenopus laevis* full length clones through EST clustering and sequence analysis.** In Proceedings of the German Conference on Bioinformatics. GI Lecture Notes in Informatics, Discovery Note

Bioinformatics webservices and educational media

Previous and Current Research

The BiBiServ group supports internet-based collaborative research in bioinformatics. More than 30 software tools and various educational media are available online. These include tools from different areas such as RNA Structures, Genome Comparison and Primer Design, which are used more than 10,000 times each month. The BiBiServ makes tools developed by the CeBiTec groups available to the bioinformatics community. We support authors in integrating their tools into the server environment and designing both HTML-based interfaces as well as Webservices. Reliable service and user support are provided, where applicable even if the author of the tool has left Bielefeld University.

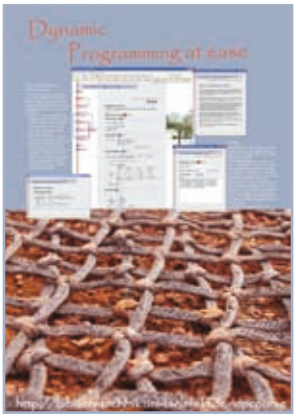
We are a member of the Helmholtz Open BioInformatic Technologies network (HOBIT). The HOBIT initiative is dedicated to form the core of a network linking bioinformatic centers together. It is an initial organizational and technological platform for interconnection of bioinformatics activities. The aim of the network is to establish the interoperability of applications and resources in a simple way using Webservices technology. Webservices allow an easy integration of remote tools in workflows based on standardized interfaces.

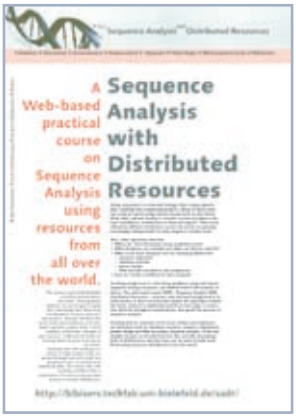
In collaboration with the Florida State University we have established *XenDB*, a database of clustered *Xenopus laevis* EST and mRNA data with special focus on the identification of full length clones. The ready availability of these full length cDNAs facilitate e.g. functional assays, one of the particular strengths of *Xenopus*.

The BiBiServ Media & Distance Education section supports teaching in bioinformatics with internet-based multimedia courses. The most recent ones are *Sequence Analysis with Distributed Resources* (a Web-based practical course on sequence analysis using resources from all over the world), *The ADP Pages* (interactive pages that allow to study and experiment with classical dynamic programming algorithms) and *About Dynamic Programming* (a gentle introduction into the technique of dynamic programming with interactive application examples).

Future Projects and Aims

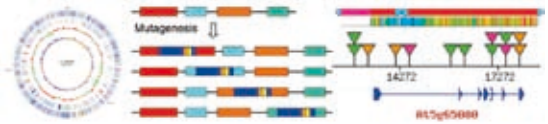
With the Webservices technology becoming more widely adopted, *in silico* experiments can be easier performed. Our goal is to provide researchers with a comfortable way to build workflows using bioinformatics tools and databases hosted on BiBiServ and other servers, and at the same time avoiding them to be concerned about interface details of the different tools. While the majority of the tools we are hosting are already available as Webservices, an effort has to be made to interconnect different services so that powerful workflows can be built on top of single tools.





Two posters announcing the Web-based courses Sequence Analysis with Distributed Resources and About Dynamic Programming, both part of the Bielefeld University Bioinformatics curriculum.

Institute for Genome Research and Systems Biology



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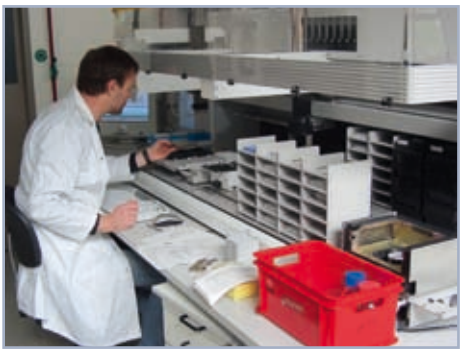
The Institute for Genome Research and Systems Biology (IGS) was founded in February 2003 when the strong performance at Bielefeld University in bacterial genomics and bioinformatics were extended in the context of the DFG Initiative 'Bioinformatics'. A new chair for Genome Research was established that complements the research on microbe genomes and plant-microbe interactions with research activities in the field of plant functional genomics (head: B. Weisshaar).

As of fall 2006, six chairs from the Faculty of Biology at Bielefeld University covering Biochemistry and Plant Physiology, Gene Technology and Microbiology, Genetics, Molecular Cell Physiology, Genome Research as well as Proteome and Metabolome Research are residing at the institute. In addition, four junior research groups are active in the areas of Transcriptomics, RNA-Based Regulation, Genomics of Legume Plants and Systems Biology of Regulatory Networks. The equipment and the research capacity of the institute is used intensively in the demanding education of BSc, MSc, and PhD students, especially for those enrolled in the programs for Bioinformatics and Genome Research as well as Genome Based Systems Biology.

The designation of the IGS initially was Institute for Genome Research. In recognition of the increasing impact and number of systems biology projects and approaches at the institute, the name was changed recently to Institute for Genome Research and Systems Biology. Among the projects that are moving towards systems biology are 'green' (plant) projects, but also several 'white' microbial research projects in which the implementation of highly sophisticated systems biology approaches is applied.

Bacteria belong to the simplest model organisms. However, it can be expected that almost all regulatory principles are implemented in these microorganisms. The bacteria under study with systems approaches all have completely sequenced genomes and can be grown on simple mineral media in the optimally controlled environment of a fermentor. This cultivation setup minimizes uncontrolled external stimuli and therefore maximizes the comparability, significance and reliability for computational systems biology analyses of the data obtained. *Corynebacterium glutamicum* is a well-established organism in industrial fermentations yielding more than a million tons of amino acids that are used in flavoring and nutrition. To further optimize biotechnological production, the regulatory connections between biomass and product formation are studied. By performing repeated cycles of comprehensive data generation, modeling and experimental testing of the hypotheses derived from the models the ultimate goal of biotechnological production becomes attainable: an engineered minimal biological system completely devoted to convert substrates to products at the theoretical yield.

Another example is the analysis of symbi-



A robotic device to load the samples for MALDI-TOF (Matrix-Assisted Laser Desorption Ionisation Time-Of-Flight; a specific type of mass spectrometry) analyses onto the target support arrays. The samples are spotted onto a metal support as an array of 96 or 384 spots. The results allow for example the identification of proteins present in the samples on the basis of molecular masses of peptides.

otic legume-microbe interactions that are characterized by the intracellular colonization of root cells by beneficial fungal or bacterial microorganisms. Both metabolic functions and signaling processes have to be tightly integrated in each organism to build functional symbiotic units. A molecular understanding of such units is facilitated by the application of genome-wide approaches for both the macro- and the microsymbiont. Ultimately, such approaches target the functional understanding of an infected, symbiotic root cell. With regard to a plant-only system, the regulatory network of transcription factors and signal transduction pathways that controls flavonoid accumulation in the *A. thaliana* seedling is studied with the goal to understand and compute the timing and the spatial control of gene regulation of the approximately 100 genes involved in a qualitative and quantitative manner.

The examples mentioned above also show that the IGS acts as a forum for communication and joint research in genomics and systems biology at Bielefeld University. These research areas rely heavily on the automation of modern molecular biology techniques which requires complex and expensive equipment. This is especially true for DNA sequencing, clone and library handling, DNA chip technology for transcriptional profiling, quantitative RT-PCR, 2D protein analyses, and mass spectrometry for protein and metabolite analyses. At the IGS, a central Technology Platform Genomics supports these and other technologies to allow high-level access to transcriptomics, proteomics and metabolomics techniques. The high-throughput data generated needs to be handled, stored, organized and analyzed. This happens together with the Bioinformatics Resource Facility (BRF) of the CeBiTec, and also in close collaboration with the colleagues of the Institute for Bioinformatics.

Contributing Units

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Prof. Dr. Rudolf Eichenlaub

Genetics
Prof. Dr. Alfred Pühler

Molecular Cell Physiology
Prof. Dr. Dorothee Staiger

Genome Research
Prof. Dr. Bernd Weisshaar

Proteome and Metabolome Research
Prof. Dr. Karsten Niehaus

Transcriptomics
HD Dr. Anke Becker

Genomics of Legume Plants
PD Dr. Helge Küster

RNA-Based Regulation
PD Dr. Thomas Merkle

Systems Biology of Regulatory Networks
Dr. Andreas Tauch

Technology Platform Genomics
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Biochemistry and Plant Physiology

Karl-Josef Dietz

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Since 1997: Professor for Biochemistry and Plant Physiology, Faculty of Biology,
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The role of the redox proteome and the cellular redox homeostasis in the general and specific stress response: a challenge for a systems' biology approach

Previous and Current Research

Stimulus-triggered biochemical and molecular-genetic responses continuously counteract the negative impact on growth and development of adverse environmental conditions such as cold, heat, excess light, heavy metal intoxication or inadequate water and nutrient supply. Two principal types of stimulus-response relationships mediate the appropriate responses and optimize growth performance: (i) Specific sensory systems detect and transmit information on changes in defined relevant environmental parameters such as cadmium exposure or heat. (ii) The second type of mechanism senses deviations from optimum cell state and triggers gradual network responses as general acclimation processes.

A large set of proteins contains oxidation-sensitive thiol-groups (3). The transition from a dithiol to the disulfide state often alters protein structure and function. All cells from any organism contain networks of interacting dithiol/disulfide transition proteins that control development, metabolism and general acclimation responses. A detailed understanding of the thiol/disulfide proteome, the interaction of its components, and its significance for the regulatory state of the cell at the levels of protein function as well as transcriptional and post-transcriptional activity will provide significant clues on how organisms counteract metabolic imbalances, differentiate distinct environmental parameters, optimize fitness and also information on the evolution of the general and specific stress response.

To reach this goal, a combination of various experimental and bioinformatics approaches is employed, e.g. (i) identification of the components of the thiol/disulfide redox proteome (3), (ii) functional analysis of thiol/disulfide transitions, (iii) targeted disturbance of the redox networks by using transgenic plants (1, 4), (iv) dissection of redox-dependent regulated promoters, their *cis*-elements and *trans*-factors and (v) elucidation of intracellular signaling networks linking the three subgenomes of the plant cell (2, 5).

The results illustrate the significance of the redox proteome for plant fitness particularly under stress, pinpoint specific triggering of responses upon disturbance, demonstrates the ability to highlight the high conservation between man/vertebrates and plants and promises new approaches for plant improvement.

Funding

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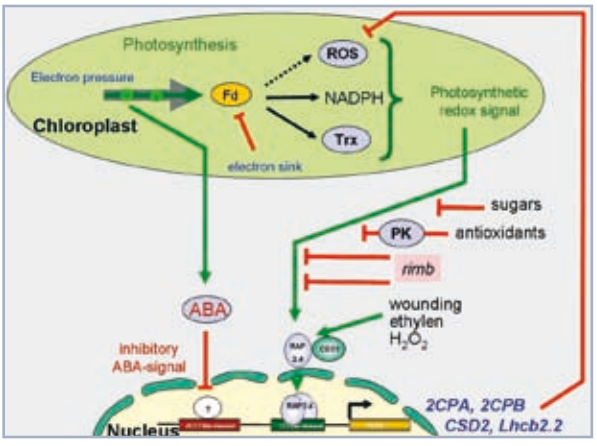

Schematic representation of the signaling network controling nuclear gene expression of 2-cysteine peroxiredoxin.

Selected publications

Lamkemeyer, P. *et al.*: 2006. PrxQ of *Arabidopsis thaliana* is attached to the thylakoids and functions in context of photosynthesis. Plant Journal, 45: 968-981

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Wormuth, D. *et al.*: 2005. Regulation of nuclear and chloroplast transcript levels by photosynthetic signals triggered through modified CO_2 availability. BMC Plant Biology, 6: 15

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Pathogenic interaction of *Clavibacter michiganensis* with tomato

Previous and Current Research

Clavibacter michiganensis subsp. *michiganensis* (*Cmm*) is a Gram-positive bacterium which causes bacterial wilt and canker in tomato plants. *Cmm* is the most important bacterial pathogen of tomato and causes severe economic losses in agriculture worldwide.

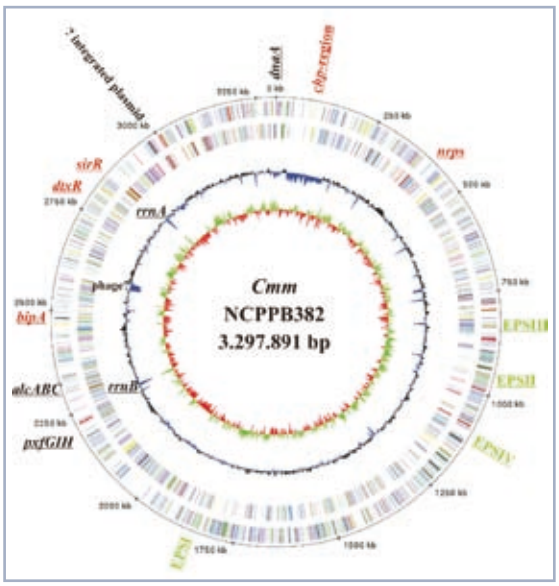
In our studies we have identified two *Cmm* genes, *pat-1* and *celA*, which are responsible for the disease in tomato. Both genes are located on plasmids. When these plasmids are lost the resulting plasmid-free *Cmm* strain is non-pathogenic but still able to infect and to colonize tomato plants. This endophytic phenotype can be reverted to pathogenicity by cloning of the *pat-1* or *celA* genes into the plasmid-free strain.

Recently, the complete nucleotide sequence of *Cmm* has been determined here in Bielefeld. The analysis of the sequence information has revealed a pathogenicity island in the genome which was detected by its low G+C content of the DNA. In this region there are numerous genes for serine-proteases. Knock-out mutations in several of these protease-genes showed that they are involved in the plant-microbe interaction.

Future Projects and Aims

The main goal of our work is to identify and understand the function of all the genes of the bacterium that are involved in the pathogenic interaction with the host plant tomato. By proteome and transcriptome analysis we try to identify genes which are specifically expressed in the interaction with the plant. Such genes are then inactivated and the pathogenic phenotype of these *Cmm* mutants is tested.

In the future the data will allow improvements in detection and control of the pathogen in agriculture and eventually provide new approaches for the generation of tomato cultivars that are resistant or tolerant against *Clavibacter michiganensis* subsp. *michiganensis*.



The genome of *Clavibacter michiganensis* subsp. *michiganensis*.

Selected publications

Eichenlaub, R. *et al.*: 2006. ***Clavibacter michiganensis*, a group of Gram-positive phytopathogenic bacteria.** In: Plant-associated Bacteria, Samuel Gnanamanickam (Ed.), Springer, pp. 385-421

Burger, A. *et al.*: 2005. **Identification of homologues to the pathogenicity factor Pat-1, a putative serine protease of *Clavibacter michiganensis* subsp. *michiganensis*.** Microbiol. Res., 160: 417-427

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Selected publications

Hain, T. *et al.*: 2006. Whole genome sequence of *Listeria welshimeri* reveals common steps in genome reduction with *Listeria innocua* as compared to *Listeria monocytogenes*. J. Bacteriol., 188: 7405-7415

Krause, A. *et al.*: 2006. Complete genome of the mutualistic, N_2-fixing grass endophyte *Azoarcus sp.* strain BH72. Nat. Biotechnol., 24: 1385-1391

Schneiker, S. *et al.*: 2006. Genome sequence of the ubiquitous hydrocarbon-degrading marine bacterium *Alcanivorax borkumensis*. Nat. Biotechnol., 24: 997-1004

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Tauch, A. *et al.*: 2005. Complete genome sequence and analysis of the multiresistant nosocomial pathogen *Corynebacterium jeikeium* K411, a lipid-requiring bacterium of the human skin flora. J. Bacteriol., 187: 4671-4682

Thieme, F. *et al.*: 2005. Insights into genome plasticity and pathogenicity of the plant pathogenic bacterium *Xanthomonas campestris* pv. vesicatoria revealed by the complete genome sequence. J. Bacteriol., 187: 7254-7266

Genome research on bacteria relevant for agriculture, environment, and biotechnology

Previous and Current Research

An overview on bacterial genomes sequenced up to now by the Chair of Genetics is presented in Table 1. In 2001, the sequences of the first two genomes, namely those of *S. meliloti* 1021 and *C. glutamicum* ATCC 13032 could be completed. The soil bacterium *S. meliloti* is well-known for its capacity to fix atmospheric nitrogen in symbiosis with its host plant *Medicago*. In contrast to *S. meliloti* which plays a role in agriculture, *C. glutamicum* is of industrial interest, since it is used world-wide for the production of amino acids mostly employed as feed additives. Finally, the Chair of Genetics is involved in the analysis of the soil bacterium *X. campestris* pv. campestris which is known as a phytopathogen for crucifers but also as an industrial producer of the polysaccharide xanthan. In the meantime, the genome sequence of *X. campestris* pv. campestris B100 is completed and will be published in the near future.

The research work performed by the Chair of Genetics is financially supported by grants from different sources, e.g. by the Ministry of Education and Research concerning the GenoMik-Plus network entitled 'Genome Research on Bacteria relevant for Agriculture, Environment and Biotechnology'. The structure of the network composed of more than 20 groups from universities, research institutes and companies is presented in Fig. 1. The GenoMik-Plus network is coordinated by Bielefeld University, also hosting a technology platform for bioinformatics, transcriptomics, proteomics, and metabolomics.

Future Projects and Aims

Comparative genomics concerning xanthomonads, sinorhizobia, and coryneform bacteria is one of the future goals. For this reason, the Chair of Genetics started to introduce the ultrafast sequencing techniques which was already applied to sequence *Corynebacterium urealyticum* and *Sinorhizobium meliloti* SM11 *de novo*. A further goal concerns the comprehensive analysis of antibiotic resistance plasmids isolated from the microbial community of wastewater treatment plants. Finally, the Chair of Genetics is heavily engaged in setting up a genome based systems biology for industrially used bacteria, in particular for *C. glutamicum* and *X. campestris* pv. campestris.

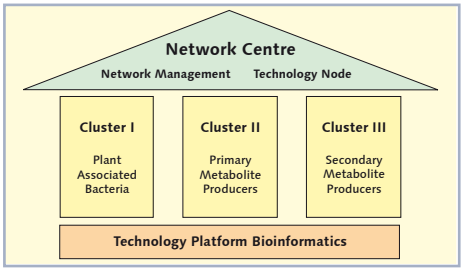

Fig. 1: Structure of the GenoMik-Plus network.

Table 1: Bacterial genomes sequenced at the Chair of Genetics in frame of the BMBF-Competence Network.

Organism	Size	Reference
Sinorhizobium meliloti 1021	6.68 Mb	Galibert *et al.*: 2001
Corynebacterium glutamicum ATCC 13032	3.28 Mb	Kalinowski *et al.*: 2003
Xanthomonas campestris pv. campestris B100	5.50 Mb	Vorhölter *et al.*: 2003
Corynebacterium jeikeium K411	2.46 Mb	Tauch *et al.*: 2005
Xanthomonas campestris pv. vesicatoria 85-10	5.18 Mb	Thieme *et al.*: 2005
Alcanivorax borkumensis SK2	3.12 Mb	Schneiker *et al.*: 2006
Azoarcus sp. BH72	4.38 Mb	Krause *et al.*: 2006
Clavibacter michiganensis subsp. *michiganensis*	3.30 Mb	in progress
Sorangium cellulosum So ce56	13.01 Mb	in progress

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Regulatory networks within the circadian timing system

Previous and Current Research

We are interested in the molecular basis of biological timekeeping. Higher plants, like most organisms, are equipped with an endogenous timing mechanism, the so-called biological or 'circadian' clock. This clock enables plants to anticipate sunrise and sunset and to adjust developmental programs like the transition to flowering to the appropriate season of the year. Our research mainly focuses on the characterization of an RNA-binding protein, *At*GRP7, in the circadian system of *Arabidopsis thaliana*. We have shown that this protein is part of a negative post-transcriptional feedback loop and represents the first example of a molecular slave oscillator. This slave oscillator is involved in signal transduction within a clock output pathway by controlling downstream targets.

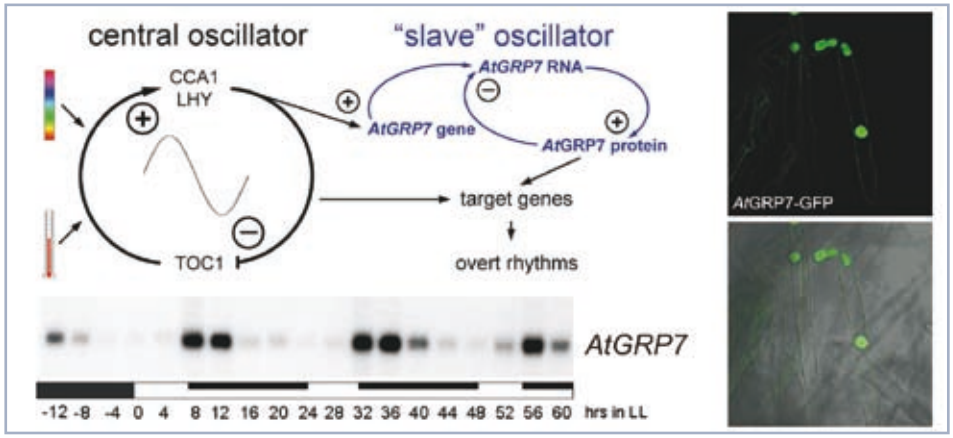
Future Projects and Aims

To identify target transcripts, we perform parallel transcript profiling of wild-type plants and plants with altered *At*GRP7 levels. Using bioinformatics tools we aim to identify common *cis*-regulatory motifs within the transcribed region that mediate post-transcriptional control. This will serve to unravel the regulatory network downstream of this RNA-binding protein at a systems level.

Transgenic plants with altered *At*GRP7 levels are also used to study its impact on physiological traits like stress responses and the transition to flowering. This may lead to important insights how to manipulate the timing of flowering which may ultimately be transferred to agronomically important plants.

Furthermore, we use the interaction of the RNA-binding protein with its own RNA as a model to develop new techniques to measure RNA-protein interaction at the level of single molecules based on Fluorescence Correlation Spectroscopy using synthetic RNA oligonucleotides labeled with fluorescent dyes (with Prof. Markus Sauer) and atomic force microscopy (with Prof. Dario Anselmetti).

Since the RNA-binding protein controls both splicing (in the nucleus) and RNA stability (in the cytoplasm) we also develop a system based on fluorescent reporters to monitor nucleo-cytoplasmic shuttling of *At*GRP7 in transiently agroinfected *Nicotiana benthaminiana* leaves and stably transformed *Arabidopsis thaliana* plants.



The evening-specific, nuclear-localized AtGRP7 protein transduces circadian timing information upon target transcripts (Jan C. Schöning and Martina Lummer).

Selected publications

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Rudolf, F. *et al.*: 2004. **Slave to the rhythm.** The Biochemist, 26: 11-13

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Staiger, D. *et al.*: 2003. **The circadian clock regulated RNA-binding protein AtGRP7 autoregulates its expression by influencing alternative splicing of its own pre-mRNA.** Plant J., 33: 361-371

Ziemienowicz, A. *et al.*: 2003. ***Arabidopsis* transportin1 is the nuclear import receptor for the circadian clock-regulated RNA-binding protein *At*GRP7.** Plant Mol. Biol., 53: 201-212

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Selected publications

Li, Y. *et al*.: 2006. **GABI-Kat SimpleSearch: an *Arabidopsis thaliana* T-DNA mutant database with detailed information for confirmed insertions.** Nucleic Acids Res., in press

Li, Y. *et al*.: 2006. **Analysis of T-DNA insertion site distribution patterns in *Arabidopsis thaliana* reveals special features of genes without insertions.** Genomics, 87: 645-652

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Rosso, M.G. *et al*.: 2003. **An *Arabidopsis thaliana* T-DNA mutagenized population (GABI-Kat) for flanking sequence tag-based reverse genetics.** Plant Mol. Biol., 53: 247-259

Strizhov, N. *et al*.: 2003. **High-throughput generation of sequence indexes from T-DNA mutagenized *Arabidopsis thaliana* lines.** BioTechniques, 35: 1164-1168

A tool for functional genomics and reverse genetics in *Arabidopsis thaliana*: the GABI-Kat T-DNA insertion collection

Previous and Current Research

The Chair of Genome Research is dedicated to functional genomics for identification of new gene activities, and aims to transfer knowledge from the model system *A. thaliana* to crop plants. Activities at the chair include projects to unravel regulatory networks of transcription factors controlling phenylpropanoid biosynthesis, a project to determine the genome structure of sugar beet, 454 sequencing of plant genomes and transcriptomes, and also the GABI-Kat project that is detailed below.

In model organisms like yeast or mouse, directed mutagenesis of selected genes by homologous recombination is an important method to assign functions to genes. For higher plants, however, this is not feasible. GABI-Kat is one of the leading projects world-wide that attempts to overcome this problem. The project is a part of the German Plant Genome Research Program GABI (Genomanalyse im biologischen System Pflanze) and generates a collection of sequence-indexed insertion mutants that are used as tools for reverse genetic experimental approaches.

In *A. thaliana* insertion mutants can be created easily using *Agrobacterium tumefaciens* T-DNA as a mutagen. DNA sequences spanning the border between the T-DNA and host genomic DNA are generated by PCR-based methods. Border sequences are evaluated based on the complete *A. thaliana* genome and insertion sites are mapped to annotated genes. So far, more then 93,000 insertion lines were created and characterized. More than 109,500 sequences were made publicly available through databases like EMBLdb or GenBank. This makes GABI-Kat the largest T-DNA population in Europe and the second world-wide. For about 2,100 *A. thaliana* genes, lines with insertions in their coding sequence are available from GABI-Kat only.

Future Projects and Aims

So far, about 4,300 different lines have been delivered to scientists all over the world. The project home page (http://www.GABI-Kat.de/) currently lists 86 publications that have used GABI-Kat material. Since 2005 GABI-Kat lines have become freely available to the international research community and the most relevant GABI-Kat lines are transferred to the Nottingham Arabidopsis Stock Centre. More than 58,000 seed stocks representing about 4,000 original lines have been donated already. The relieved access conditions have resulted in an intensified use of the GABI-Kat insertion mutants. Alleles from the GABI-Kat population make a significant contribution to saturate the *A. thaliana* genome, which contains about 30,000 protein-coding genes, with NULL mutations. The ultimate goal is to use the new knowledge obtained from the model system *A. thaliana* to further improve today's food crops.

Wall cress (*Arabidopsis thaliana*) in culture. During growth in the greenhouse (younger plants in front, older ones in the background), plants have to be attached to wooden rods to finally allow collection of seeds from individuals.

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2005: Professor for Proteome and Metabolome Research, Bielefeld University, Germany

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Post-genome research to understand the molecular basis of plant-microbe interactions

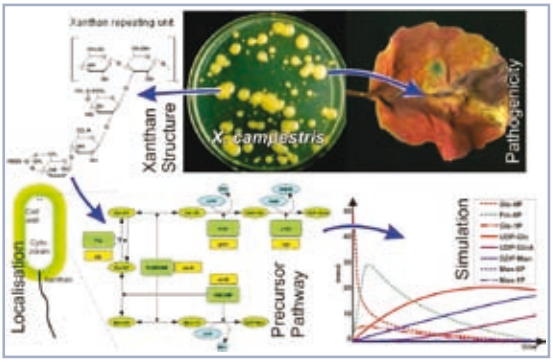
Previous and Current Research

The Department for Proteome and Metabolome Research has a strong focus on interdisciplinary approaches in the field of bacterial metabolism and the analysis of plant-microbe interaction on a molecular level. A second line of work focuses on the analysis of the plants signal transduction network connected to the plant-microbe interaction. As the nomination indicates, our research is based on advanced proteome and metabolome methods which also include state of the art imaging techniques. The proteome subgroup utilizes two-dimensional gel electrophoresis and mass spectrometry-based identification techniques for a differential display of proteins from microbe and plant tissues.

In an early approach the analysis of the extracellular proteins of the phytopathogen *Xanthomonas campestris* pv. campestris (*Xcc*) lead to the identification of novel virulence factors in the interaction with non-host plants like tobacco. This first glance at the extracellular proteome opened a new field of research in which outer membrane vesicles are investigated as vehicles for the delivery of virulence factors into the host system. Embedded in this line of research we also investigate the impact of lipopolysaccharides (LPS) which are perceived by host and non-host plants of *Xcc*. Pathogen derived LPS triggers a GTPase activated NADPH-oxidase, which mounts an oxidative burst reaction as part of a defense reaction, on the plant cell surface. In contrast, the LPS isolated from the symbiotic soil bacterium *Sinorhizobium meliloti* is able to suppress defense reactions of the host plant. The high-throughput localization of proteins in living cells aids our understanding of structural changes which take place within plant cells upon confrontation with microbes. Metabolome studies from both interaction partners give insights into how the microbe and the plant host rearrange their metabolism to adjust themselves to the given interaction. The simultaneous research on both the symbiotic and pathogenic plant-microbe interaction will enable us to understand not only the fundamental differences which enables the plant to distinguish between 'friend and foe' but also how the microbe manages to evade the recognition of the plants innate immune system to propagate disease symptoms in host plants.

Future Projects and Aims

The obvious vision is now to go from genes to functions in order to describe the behaviour of entire systems. Realizing the potential of post-genome science will be a highly interdisciplinary process requiring close collaboration between a wide range of disciplines. Understanding of complex systems needs the integration of experimental and computational research, leading to a systems biology approach.



The phytopathogenic bacterium *Xanthomonas campestris* pv. campestris is used as a model organism for plant-microbe interactions and a systems biology approach to analyze its biotechnological potential.

Selected publications

Tellström, V. *et al.*: 2007. **The lipopolysaccharide of *Sinorhizobium meliloti* suppresses defense-associated gene expression in cell cultures of the host plant *Medicago truncatula*.** Plant Phys., in press

Barsch, A. *et al.*: 2006. **Metabolite profiles of nodulated alfalfa plants indicate that distinct stages of nodule organogenesis are accompanied by global physiological adaptations.** Mol. Plant-Microbe Interact., 19: 998-1013

Braun, S. *et al.*: 2005. **Characterization of the *Xanthomonas campestris* pv. campestris lipopolysaccharides substructures essential for elicitation of an oxidative burst in tobacco cells.** Mol. Plant-Microbe Interact., 18: 674-681

Watt, S. *et al.*: 2005. **Comprehensive analysis of the extracellular proteins from *Xanthomonas campestris* pv. campestris B100.** Proteomics, 5: 153-167

Yaneva, I.A. and Niehaus, K.: 2005. **Molecular cloning and characterisation of a Rab-binding GDP-dissociation inhibitor from *Medicago truncatula*.** Plant Physiol. Biochem., 43: 203-212

Kunze, G. *et al.*: 2004. **The N terminus of bacterial elongation factor Tu elicits innate immunity in *Arabidopsis* plants.** Plant Cell, 16: 3496-3507

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Selected publications

Pobigaylo, N. *et al.*: 2006. Construction of a large sequence signature-tagged miniTn*5* transposon library and its application to mutagenesis of *Sinorhizobium meliloti*. Appl. Environ. Microbiol., 72: 4329-4337

Hohnjec, N. *et al.*: 2005. Overlaps in the transcriptional profiles of *Medicago truncatula* roots inoculated with two different *Glomus* spec. fungi provide insights into the genetic program activated during arbuscular mycorrhiza. Plant Physiol., 137: 1283-1301

Sharypova, L. *et al.*: 2005. Overproduction and increased molecular weight account for the symbiotic activity of the *rkpZ*-modified K polysaccharide from *Sinorhizobium meliloti* Rm1021. Glycobiology, 16: 1181-1193

Becker, A. *et al.*: 2004. Global changes in gene expression in *Sinorhizobium meliloti* 1021 under microoxic and symbiotic conditions. Mol. Plant-Microbe Interact., 17: 292-203

Hoang, H. *et al.*: 2004. The LuxR homolog ExpR, in combination with the Sin quorum sensing system, plays a central role in *Sinorhizobium meliloti* gene expression. J. Bacteriol., 186: 5460-5472

Krol, L. and Becker, A.: 2004. Global transcriptional analysis of phosphate stress responses in *Sinorhizobium meliloti* strains 1021 and 2011. Mol. Gen. Genomics, 272: 1-17

Functional genomics of plant-associated bacteria

Previous and Current Research

The research group is interested in symbiotic plant-microbe interactions and bacterial polysaccharide production. The studies mainly focus on the soil bacteria *Sinorhizobium meliloti* and *Xanthomonas campestris* pv. campestris. *S. meliloti* enters a symbiosis with certain leguminous plants including the model legume plant *Medicago truncatula*. This symbiotic interaction leads to the formation of root nodules that house nitrogen-fixing rhizobial cells. The Rhizobium-legume symbiosis is a major source for fixed nitrogen and therefore important for sustainable agriculture. This interaction is studied applying genomic and post-genomic strategies including '-omics' and mutagenesis approaches. Fig. 1 shows the application of a *S. meliloti* signature-tagged transposon mutant library for high-throughput identification of genes relevant for competitiveness and symbiosis.
X. campestris pv. campestris is a phytopathogenic bacterium that is well-known for its ability to synthesize the polysaccharide xanthan. This polysaccharide is produced in a biotechnological process and applied as a thickener and stabilizing agent. Transcriptome methods are applied to monitor global gene expression profiles with the aim to optimize the production process.

Future Projects and Aims

Small non-coding RNAs make a major contribution to regulation in prokaryotic cells. In rhizobia these regulatory RNAs are widely unknown. The objective of future projects is a comprehensive identification of these RNAs in *S. meliloti* as well as understanding their role in symbiosis and adaptation to stress conditions. A further objective is the generation of a genome-wide promoter and operon map in *S. meliloti* as a basis for a better understanding of genome wide regulatory networks that control gene transcription. A future challenge is also the investigation of the *in planta* transcriptome of symbiotic bacteria at the level of defined plant tissue areas or even single plant cells.

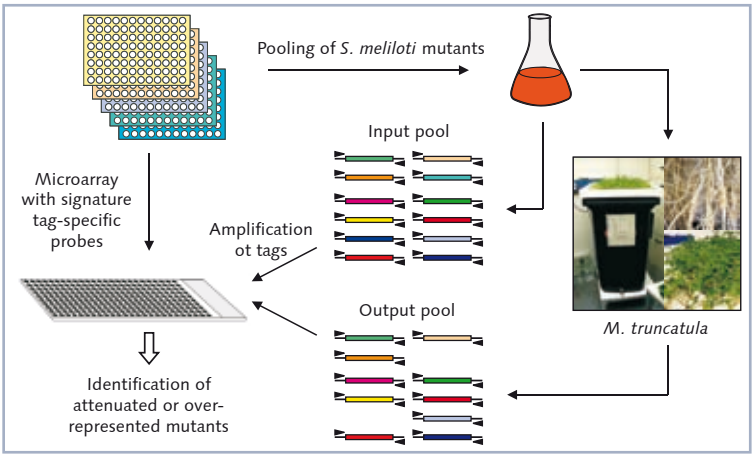

Fig. 1: Screening of a signature-tagged *S. meliloti* mutant library. Pools of *S. meliloti* mutants are screened for competitiveness in symbiosis. Each mutant of a pool is individually marked by a short unique sequence signature tag. Identification and quantification of the mutants in the input and output pools of the experiment is performed by quantification of the tags by microarray hybridization.

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Transcriptomics-based dissection of legume endosymbioses

Previous and Current Research

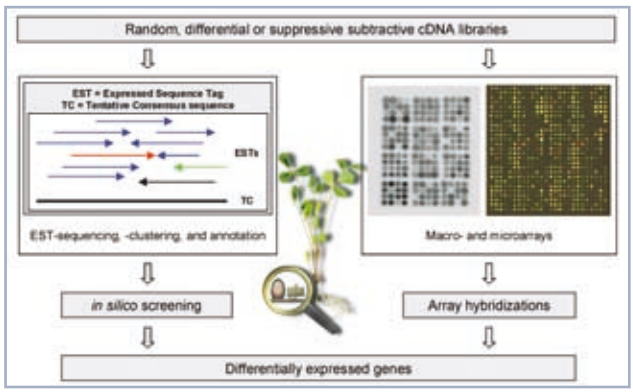
Legume plants have the remarkable capacity to enter beneficial root endosymbioses with soil microorganisms: The formation of root nodules in symbiosis with *Sinorhizobium meliloti* and the arbuscular mycorrhiza (AM) interaction with *Glomus* spec. fungi. Nodulation leads to biological nitrogen fixation, and AM improves uptake of phosphorus from the soil. Biological nitrogen fixation allows the formation of protein-rich tissues, e.g. the seeds of grain legumes. Due to these properties, grain legumes, perennial herbaceous legumes, and legume trees are excellent resources for the sustainable production of food, feed, fibres and fuels.

The group pursues transcriptomics in the model plant *Medicago truncatula* to study legume biology. We performed high-throughput EST-sequencing and established an Mt16kOLI1Plus 70mer oligo microarray platform that covers appr. 35 % of the estimated *M. truncatula* gene space. Together with the BRF, Web-based bioinformatics tools for storage and evaluation of expression profiling data were developed. Based on our microarrays, some 1000 hybridization experiments were performed in different projects (TRUNCATULIX portal, http://www.cebitec.uni-bielefeld.de/groups/glp/truncatulix).

A major focus of the group is the molecular analysis of AM. In the SPP1084 'MolMyk: Molecular Basics of Mycorrhizal Symbioses', we applied *in silico* and microarray-based expression profiling to identify a core set of genes reproducibly induced in different AM interactions, including several genes whose expression was specifically localized in arbuscule-containing cells. Using laser capture microdissection, a cellular expression profile of nitrogen-fixing root nodules was established. From the comparison of expression profiles, a collection of genes activated in either symbiosis was identified, and selected 'symbiosin' genes are characterized by reverse genetics in transgenic plants.

Future Projects and Aims

Building on our previous work using pooled AM tissues, we now focus our activities on specific cells to allow a correlation of expression profiles with the two characteristic stages of AM: epidermal cells in contact with the fungal appressoria that mediate hyphal penetration and cortical cells harbouring arbuscules, specialized fungal structures dedicated to nutrient exchange. In these experiments, gene expression for the first time will be studied both in the macro- and the microsymbiont, based on whole-genome GeneChips. Bidirectional exchange of signals takes place during all stages of AM development, and based on the expression profiles obtained, reverse genetics analyses will decipher signal transduction events relevant for establishment and maintenance of AM.



Discovery science: The model plant *Medicago truncatula* is used to study legume biology by combining in silico and experimental transcriptome profiling approaches. Differentially expressed genes identified by transcriptomics are subsequently analyzed by reverse genetics to determine biological functions.

Selected publications

Hohnjec, N. *et al.*: 2006. **Transcriptional snapshots provide insights into the molecular basis of arbuscular mycorrhiza in the model legume *Medicago truncatula*.** Funct. Plant. Biol., 33: 737-748

Barsch, A. *et al.*: 2006. **Metabolite profiles of nodulated alfalfa plants indicate that distinct stages of nodule organogenesis are accompanied by global physiological adaptations.** Mol. Plant-Microbe Interact., 19: 998-1013

Hohnjec, N. *et al.*: 2005. **Overlaps in the transcriptional profiles of *Medicago truncatula* roots inoculated with two different *Glomus* fungi provide insights into the genetic program activated during arbuscular mycorrhiza.** Plant Physiol., 137: 1283-1301

El Yahyaoui, F. *et al.*: 2004. **Expression profiling in *Medicago truncatula* identifies more than 750 genes differentially expressed during nodulation, including many potential regulators of the symbiotic program.** Plant Physiol., 136: 3159-3176

Manthey, K. *et al.*: 2004. **Transcriptome profiling in root nodules and arbuscular mycorrhiza identifies a collection of novel genes induced during *Medicago truncatula* root endosymbioses.** Mol. Plant-Microbe Interact., 17: 1063-1077

Thomas Merkle

1991: PhD, University of Freiburg, Germany
1992-1996: Postdoctoral position, Friedrich Miescher-Institute in Basel, Switzerland, and University of Colorado at Boulder, U.S.A.
2002: Habilitation in Cell Biology, University of Freiburg, Germany
2002-2003: Professor for Plant Developmental Physiology, University of Kiel, Germany
Since 2004: Leader of the Junior Research Group RNA-Based Regulation,
Bielefeld University, Germany

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Selected publications

Martini, J. *et al*.: 2007. Multifocal two-photon laser scanning microscopy combined with photo-activatable GFP for *in vivo* monitoring intracellular protein dynamics in real time. J. Struct. Biol., in press

Grasser, M. *et al*.: 2006. The *Arabidopsis* genome encodes structurally and functionally diverse HMGB-type proteins. J. Mol. Biol., 358: 654-664

Kaminaka, H. *et al*.: 2006. bZIP10-LSD1 antagonism modulates basal defense and cell death in *Arabidopsis* following infection. EMBO J., 25: 4400-4411

Launholt, D. *et al*.: 2006. Chromatin-associated HMGA and HMGB proteins use different signals for nuclear targeting and display a highly dynamic localisation within the cell nucleus. Plant Cell, 18: 2904-2918

Merkle, T.: 2003. Nucleo-cytoplasmic partitioning of proteins in plants: implications for the regulation of environmental and developmental signalling. Curr. Genet., 44: 231-260

Regulation of signaling by microRNAs and nuclear export

Previous and Current Research

The group is interested in two regulatory mechanisms that are important for the fine tuning of gene expression and signaling: i) microRNA-directed cleavage of specific mRNAs as a tool to post-transcriptionally control gene expression and ii) nucleo-cytoplasmic partitioning of transcription factors as a means to post-translationally regulate signaling. These regulatory mechanisms enable plants to quickly respond to changing environmental conditions and to adjust their developmental programs.

In cooperation with Marc Rehmsmeier's group we have optimized microRNA target prediction algorithms for plants and predicted several novel microRNA targets in *A. thaliana* that encode transcription factors or other regulatory proteins. Many of these were experimentally validated as novel microRNA targets in *A. thaliana*. On the other hand we have functionally characterized important proteins that regulate nuclear transport in plants. We have used this knowledge to identify proteins that are exported from the nucleus as a means to switch off signaling. We are employing genetic and cell molecular biological tools to characterize the function of the genes / proteins that are targeted by these regulatory mechanisms.

Future Projects and Aims

We are investigating the function of selected novel microRNA targets including genes that encode MYB transcription factors as well as a novel protein that is not functionally characterized to date. Over-expression of microRNA-resistant mRNA versions in transgenic plants resulted in dramatic phenotypic effects that are very similar and most prominent in leaves. Characterizing the target genes of the MYB transcription factors and the genetic interaction with the as yet uncharacterized gene will help us to shed light on this novel regulatory circuit.

In the second project we identified many proteins that are exported from the nucleus and that belong to different protein classes. Many of them are transcription factors that function in the nucleus. Several proteins containing a nuclear export signal were selected for further functional characterization that aims at the understanding of the role of nuclear export for the regulation signal transduction.

Cooperations

Marc Rehmsmeier, Bioinformatics of Regulation, Bielefeld; Dario Anselmetti, Experimental Biophysics and Applied Nanoscience, Bielefeld; Klaus Harter, University of Tübingen, Germany; Klaus D. Grasser, University of Aalborg, Denmark

Functional analysis of an *Arabidopsis thaliana* gene encoding a novel regulatory protein that is targeted by a microRNA. Phenotypic effects of the over-expression of the unmodified (B) and of a microRNA-resistant mRNA (C) in transgenic *Arabidopsis* plants as compared to a wild type plant (A).

Andreas Tauch

1996: PhD, Bielefeld University, Germany
1997: Postdoctoral position at the Degussa AG, Halle/Westfalen, Germany
2000: Postdoctoral position, Technology Platform Genomics, CeBiTec, Bielefeld University, Germany
2006: Leader of the Junior Research Group Systems Biology of Regulatory Networks, CeBiTec, Bielefeld University, Germany

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Reconstruction of the transcriptional regulatory networks of Corynebacteria

Previous and Current Research

The genus *Corynebacterium* is a diverse collection of Gram-positive bacteria, including species of industrial interest as well as human and animal pathogens. The availability of sequenced corynebacterial genomes provides the basis to conduct systematic studies on gene regulatory systems. Using a combination of several computational methods, the repertoire of DNA-binding transcriptional regulators in corynebacteria was estimated and characterized. This repertoire defined the core set of transcription factors encoded in corynebacteria and contributed to the development of a hierarchical and modular network model. The current information on transcriptional regulation was compiled and organized in the specialized database CoryneRegNet that supports global network reconstruction. The genomic data together with DNA microarray hybridization has moreover opened the way for genome-scale experimental reconstruction of transcriptional regulatory networks (Fig. 1). The research work of the Systems Biology of Regulatory Networks group is supported by the International Graduate School in Bioinformatics and Genome Research (Germany), the CAPES Foundation (Brazil), Roche Applied Science (Germany) and Unilever R&D (UK).

Future Projects and Aims

Comprehensive comparative genomics of a larger set of corynebacteria is the aim of future work, to provide not only insights into the common architecture of the genomes but also into the evolution of the gene regulatory networks. Therefore, ultrafast *de novo* sequencing of two corynebacteria was recently performed with the Genome Sequencer 20 System. A further project concerns the genome-wide transcriptional analysis of a skin corynebacterium to elucidate its role in body odor formation.

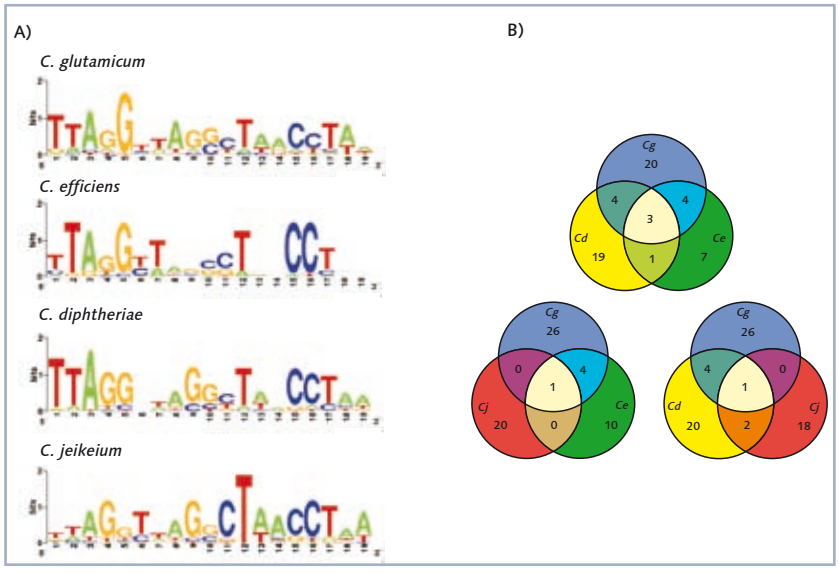

Fig. 1: Comparative analysis of DNA-binding sites (A) and the gene content (B) of DtxR regulons in corynebacteria.

Selected publications

Brinkrolf, K. *et al.*: 2007. The transcriptional regulatory network of the amino acid producer *Corynebacterium glutamicum*. J. Biotechnol., in press

Brune, I. *et al.*: 2006. The DtxR protein acting as dual transcriptional regulator directs a global regulatory network involved in iron metabolism of *Corynebacterium glutamicum*. BMC Genomics, 7: 21

Tauch, A. *et al.*: 2006. Ultrafast *de novo* sequencing of *Corynebacterium urealyticum* using the Genome Sequencer 20 System. Biochemica, 4: 4-6

Brune, I. *et al.*: 2005. The individual and common repertoire of DNA-binding transcriptional regulators of *Corynebacterium glutamicum*, *Corynebacterium efficiens*, *Corynebacterium diphtheriae* and *Corynebacterium jeikeium* deduced from the complete genome sequences. BMC Genomics, 6: 86

Tauch, A. *et al.*: 2005. Complete genome sequence and analysis of the multiresistant nosocomial pathogen *Corynebacterium jeikeium* K411, a lipid-requiring bacterium of the human skin flora. J. Bacteriol., 187: 4671-4682

Jörn Kalinowski

1995: Diploma in Biology, Bielefeld University, Germany
1990: PhD in Biology, Bielefeld University, Germany
Since 2000: Head of the Technology Platform Genomics, Institute for Genome Research and Systems Biology, Bielefeld University, Germany

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Selected publications

Hansmeier, N. *et al.*: 2006. The surface (S)-layer gene *cspB* of *Corynebacterium glutamicum* is transcriptionally activated by a LuxR-type regulator and located on a 6 kb genomic island absent from the type strain ATCC 13032. Microbiology, 152: 923-935

Hansmeier, N. *et al.*: 2006. The cytosolic, cell surface and extracellular proteomes of the biotechnologically important soil bacterium *Corynebacterium efficiens* YS- 314 in comparison to those of *Corynebacterium glutamicum* ATCC 13032. Proteomics, 6: 233-250

Mormann, S. *et al.*: 2006. Random mutagenesis in *Corynebacterium glutamicum* ATCC 13032 using an IS*6100*-based transposon vector identified the last unknown gene in the histidine biosynthesis pathway. BMC Genomics, 7: 205.

Koch, D.J. *et al.*: 2005. The transcriptional regulator SsuR activates expression of the *Corynebacterium glutamicum* sulphonate utilization genes in the absence of sulphate. Mol. Microbiol., 58: 480-494

Rey, D.A. *et al.*: 2005. The McbR repressor modulated by the effector substance *S*-adenosylhomocysteine controls directly the transcription of a regulon involved in sulphur metabolism of *Corynebacterium glutamicum* ATCC 13032. Mol. Microbiol., 56: 871-887

Functional genome analysis and systems biotechnology of *Corynebacterium glutamicum*

Previous and Current Research

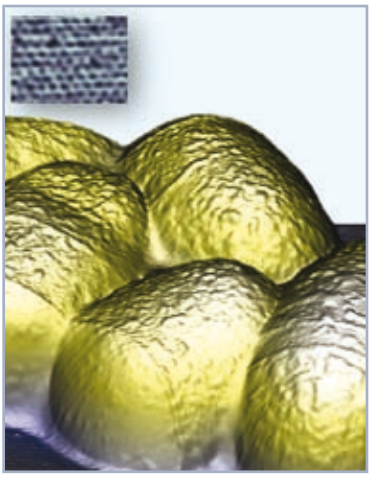
The Gram-positive soil bacterium *C. glutamicum* is a biotechnologically important microbe and used for the industrial production of amino acids by fermentation. Since the year 1985 the research group was involved in the development of genetic engineering techniques for *C. glutamicum* and in the cloning and analysis of genes from amino acid and vitamin metabolism. This research entered the genome phase in the late 1990s when we started the sequencing of the whole 3.3 megabase genome together with Degussa company. With the publication of the sequence in the year 2003, research entered the post-genomic phase and transcriptomics as well as proteomics tools and techniques for the functional genome analysis of corynebacteria were developed. By using these methods we currently focus on the genome-wide analysis of transcriptional regulatory networks and their key elements, sigma factors, transcriptional regulators and the stringent control. A second focus is on the metabolism of the macroelement sulfur and the formation of the sulfur-containing amino acid L-methionine.

Future Projects and Aims

Our aims are to understand gene functions and global regulatory networks in corynebacteria and their effects on the formation of primary metabolites, such as amino acids and vitamins. With the recent establishment of metabolomics in our lab, all comprehensive techniques are now at hand to measure the components of microbial cells. In cooperation with highly developed bioinformatics, these high-throughput data will be integrated with expression and phenotypic data in order to obtain models for systems biology. Together with genetic and genomic engineering techniques these models will then help to optimize *C. glutamicum* for different biotechnological production processes.

Cooperations

The group cooperates with academic partners from the University of Cologne (Biochemistry – R. Krämer), the University of Erlangen-Nürnberg (Microbiology – A. Burkovski), the University of Münster (Molecular Microbiology and Biotechnology – V. F. Wendisch), the University of Siegen (Simulation in Systems Engineering – W. Wiechert), the University of Ulm (Microbiology and Biotechnology – B. J. Eikmanns), and the Research Center Jülich (Biotechnology I – H. Sahm; Biotechnology II – C. Wandrey). In additon, a long-term research cooperation exists with Degussa AG (Feed Additives – K. Huthmacher, R. Kelle).



Corynebacterium glutamicum - The Golden Bug. The picture shows atomic-force microscopic images of whole cells (false colors) and of an isolated surface layer of C. glutamicum (cooperation with the Department of Experimental Biophysics & Applied Nanoscience, Bielefeld University - D. Anselmetti, R. Ros).

Bielefeld Institute for Biophysics and Nanoscience

BINAS
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for Biophysics and Nanoscience

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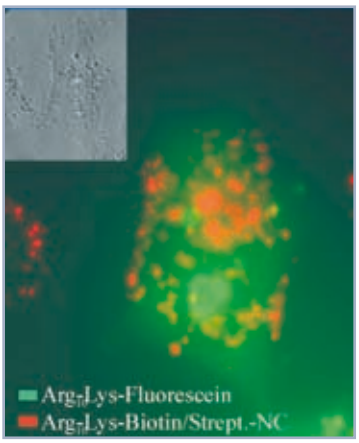
The Bielefeld Institute for Biophysics and Nanoscience (BINAS) was founded in 2004 to centralize the activities of the Bielefeld University in the areas of Nanoscience and Biophysics. The establishment was initiated by the physics Professors Dario Anselmetti (Experimental Biophysics and Applied Nanoscience), Armin Gölzhäuser (Physics of Supramolecular Systems), Ulrich Heinzmann (Molecular and Surface Physics), Günter Reiss (Thin Films and Nanostructures), and Markus Sauer (Applied Laser Physics and Laser Spectroscopy).
Nanoscience and Biophysics belong to modern research areas relevant for information technology, biomedical optics and physical engineering, all critically relying on the fruitful cooperation between different classical disciplines. Therefore, successful work of BINAS bases upon a close interdisciplinary collaboration between scientists from the Faculties of Physics, Biology, Chemistry, and Technology of Bielefeld University. Besides cooperation with the 'Industrie- und Handelskammern' Ostwestfalen, Bielefeld, Lippe, and Detmold BINAS plays an important role in knowledge transfer from basic to applied sciences. In addition, BINAS aims to help interested companies to solve important and industrially relevant scientific problems. By that, BINAS intends to promote collaborative research and development projects. Furthermore, BINAS wants to discuss chances and risks of new research developments and future prospects of modern research areas with the local community and politics.

BINAS accommodates five different chairs from the Faculty of Physics and offers various techniques including modern molecular and surface physics, ultrathin films, lithography, supramolecular systems, chemical nanolithography, LEEPS microscopy, laser physics and spectroscopy, single-molecule fluorescence spectroscopy, atomic force microscopy, and molecular nanotechnology. For example, BINAS offers electron and light microscopy techniques to eluci-



Fluorescence image of a HeLa cell excited at 488 nm in PBS buffer. The inset shows a phase-contrast image of the cell. Cells were incubated with 10-8 M solution of Qdot605-streptavidin conjugates, 10-6 M biotinylated polyarginine (Arg10-Lys), and 10-6 M fluorescently labeled polyarginine (Arg10-Lys-fluorescein) for 20 min then washed. Whereas fluorescein labeled polyarginines (green) enter the cells and accumulate in the nucleoli, streptavidin-coated NCs (red) covered with biotinylated polyarginine only bind on the membrane but do not enter the cells.

date the roughness and homogeneity of surfaces down to the atomic level. Alternatively, surfaces can be modified to protect them from impurities and contaminations, or to improve their biocompatibility for medical applications. Here, again BINAS enables the well-defined modification of surfaces with atomic resolution. Likewise techniques are at hand to specifically detect proteins in gels or bacteria without external labeling strategies due to native autofluorescence. The fluorescence-based techniques exhibit superior sensitivity down to the single-molecule level and are ideally suited for the development of new assays for highly sensitive diagnostics of viral or bacterial infections and tumor detection as well as for follow up of malignant diseases. Furthermore, the institute provides new and refined coating techniques to improve storage media, to construct optical gratings, or to develop miniaturized circuitry and develops new magnetic beads for therapeutic applications as well as for data storage.

Contributing Units

Experimental Biophysics and Applied Nanoscience
Prof. Dr. Dario Anselmetti

Physics of Supramolecular Systems
Prof. Dr. Armin Gölzhäuser

Molecular and Surface Physics
Prof. Dr. Ulrich Heinzmann

Ultrafast Laser Spectroscopy
Prof. Dr. Walter Pfeiffer

Thin Films and Nanostructures
Prof. Dr. Günter Reiss

Applied Laser Physics and Laser Spectroscopy
Prof. Dr. Markus Sauer

Dario Anselmetti

1990: PhD, Experimental Physics, Basel University, Switzerland
1990: Postdoctoral position, IBM Research Laboratory, Rüschlikon, Switzerland
1992: Postdoctoral position, Basel University / Hoffmann-La Roche, Basel, Switzerland
1994-2000: Research fellow, Ciba-Geigy / Novartis / Solvias
Since 2000: Professor for Experimental Biophysics & Applied Nanoscience,
Bielefeld University, Germany
Since 2005: Member of the Northrhine-Westfalian Academy of Sciences, Düsseldorf, Germany

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Selected publications

Hellmich, W. *et al.*: 2006. **Improved native UV laser induced fluorescence detection for single cell analysis in poly(dimethylsiloxane) microfluidic devices.** Journal of Chromatography, A 1130: 195-200

Eckel, R. *et al.*: 2005. **Single molecule experiments in synthetic biology - a new approach to the affinity ranking of DNA-binding peptides.** Angewandte Chemie (Intl. Edition), 44: 3921-3924

Ros, A. *et al.*: 2005. **Brownian Motion: absolute negative particle mobility.** Nature, 436: 928

Sischka, A. *et al.*: 2005. **Molecular mechanisms and kinetics between DNA and DNA-binding ligands.** Biophysical Journal, 88: 404-411

(complete references under: www.physik.uni-bielefeld.de/biophysik/literatur.html)

Single molecule biophysics & systems nanobiology

Previous and Current Research

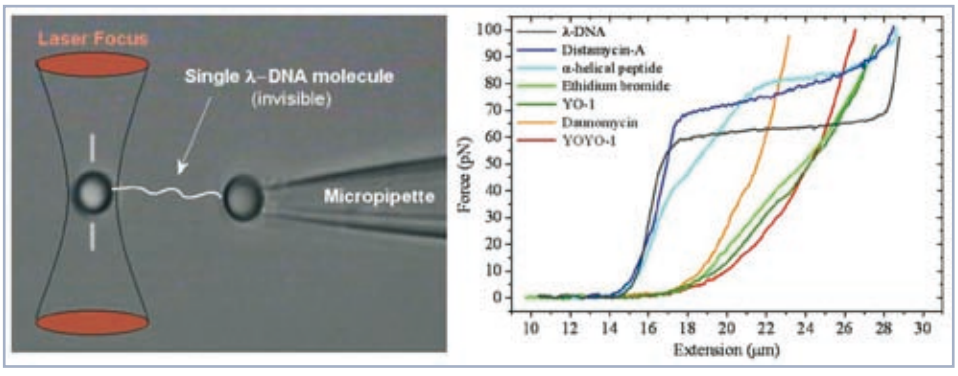
The Chair of *Experimental Biophysics & Applied Nanoscience* was founded in July 2000 at Bielefeld University with an interdisciplinary science focus on *Systems NanoBiology* with topical activities in single molecule biophysics, nano- and single cell analytics, bio- and nanophotonics and microfluidic lab-on-a-chip (see selected references).

Over the last years we developed a high stability single-beam optical tweezers (OT) system that was incorporated into an inverted light microscope which allows quantitative and analytical experiments with single molecules or cells in an experimental force range of 0.1-300 pN. Micron-sized objects like beads, colloids or cells can be trapped, steered and manipulated by light and allow force experiments on a single molecule level at a sensitivity level of 0.1 pN. With this instrument we were able to manipulate single lambda-DNA molecule between two polystyrene beads and monitor intramolecular forces in fast one-shot experiments. Upon (specific and unspecific) binding of small ligands to DNA the elastic force response of the probed DNA molecule immediately changes and allows real-time biosensoric monitoring and an identification of the corresponding binding motif (force fingerprint). This biosensor instrument is currently evaluated for rapid (physicochemical) screening of possible anti-cancer therapeutics (single molecule DNA biosensor).

In addition, detection and quantification of single, specific interaction forces between a membrane bound receptor on a living B-cell (BCR) with OT was achieved which opens new, fascinating possibilities for future single cell experiments for the functional probing of living single cells.

Future Projects and Aims

Currently we are developing a novel OT setup in a technology transfer project with a global optical company in order to supplement their optical product line.



(Left) Optical tweezer configuration as seen in light microscope. (Right) Corresponding force fingerprint of single DNA molecule experiments with DNA binding ligands.

Armin Gölzhäuser

1989: Diploma in Physics, MPI for Medical Research, Heidelberg, Germany
1993: Doctorate in Physical Chemistry, University of Heidelberg, Germany
1993-1996: Feodor Lynen Fellowship, University of Illinois, U.S.A.
2001: Habilitation in Physical Chemistry, University of Heidelberg Germany
2003: Professor for Physical Chemistry, University of Marburg, Germany
2003: Professor for Experimental Physics, Bielefeld University, Germany

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Physics of Supramolecular Systems

Supramolecular systems are aggregates of organic or biological molecules that self-assemble into larger entities (membranes, vesicles, protein complexes) *via* multiple weak interactions. One of our objectives is the fabrication and characterization of artificial supramolecular systems. An important first step towards this goal is the development of simple and rapid techniques for the site-specific immobilization of single molecules or molecular aggregates on surfaces. Such chemical surface structures play important roles in the definition of contacts in 'molecular electronics' and the miniaturization of high-throughput assays in molecular biology as well as in biosensors and tissue engineering. To fabricate chemically patterned substrates on a molecular length scale, it is necessary to modify the surface in a controlled manner with nanometer resolution. Molecular structures are created by utilizing electron beam and extended UV lithography to pattern self-assembled monolayers. Focused electron beams convert the terminal nitro functionality in self-assembled monolayers of nitrobiphenylthiol to amino groups, defining thus spatially confined reactive sites on a surface. By this electron induced chemical nanolithography ultrahigh resolution (<5 nm) templates for the site selective immobilization of molecules are created. This patterning strategy is compatible with standard microfabrication techniques and allows the efficient patterning of large areas and mass fabrication.

State-of-the-art microscopic and spectroscopic techniques are used to study specific interactions between supramolecular entities, as well as between molecules and ionizing radiation. This knowledge is utilized in the nanofabrication of surface patterns, in which individual molecules occupy distinct locations.

Artificial surfaces mimic biological functions, and are used in biosensors or biochips. More complex supramolecular entities (membranes, pores, molecular motors) can be built *via* a 'guided' self-assembly and subsequent lithographic modification on such surfaces. Recently, we have made unimolecular freestanding 'nanosheets'. These are membranes with the thickness of 1 nm and lateral sites of 100 x 100 μm^2. In technological applications, such artificial supramolecular systems can be tailored to perform specific tasks in molecular electronics, biosensors, and nanobiotechnology.

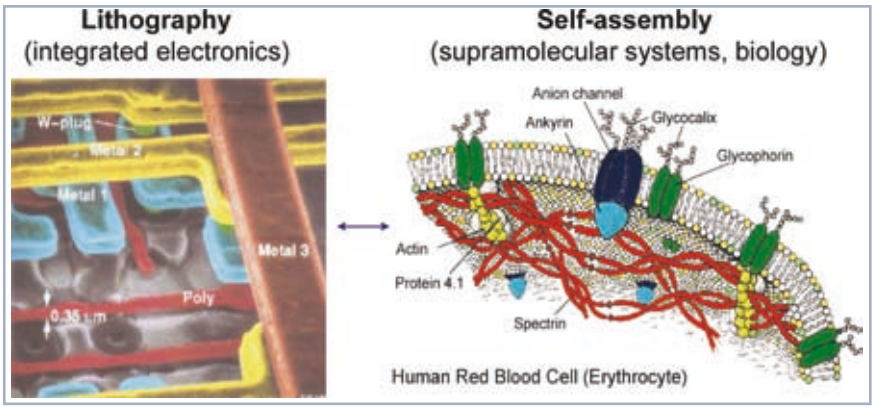

Fig. 1: Two concepts of nanostructure fabrication: Left: Integrated electronic circuits are made by lithography, i.e. a locally controlled exposure of a polymeric resist with light or electrons and a subsequent pattern transfer into silicon. Right: Biological systems spontaneously form vial self-assembly of weakly interacting molecules. We work towards the fabrication and characterization of artificial supramolecular systems by using a combination of lithography and self-assembly.

Selected publications

Bognitzki, M. *et al.*: 2006. **Preparation of sub-micrometer copper fibers *via* electrospinning**. Adv. Mat., 18: 2384-2386

He, Q. *et al.*: 2006. **Self-assembled molecular pattern by chemical lithography and interfacial chemical reactions.** J. of Nanosci. Nanotechnol., 6: 1838-1841

Eck, W. *et al.*: 2005. **Free-standing nanosheets from cross-linked biphenyl self-assembled monolayers**. Adv. Mat., 17: 2583-2587

Völkel, B. *et al.*: 2005. **Electrodeposition of copper and cobalt nanostructures using self-assembled monolayer templates**. Surf. Sci., 597: 32-41

Biebricher, A. *et al.*: 2004. **Controlled three-dimensional immobilization of biomolecules on chemically patterned surfaces**. J. Biotechnol., 112: 97-107

Küller, A. *et al.*: 2003. **Nanostructuring of silicon by electron beam lithography of self-assembled hydroxybiphenyl monolayers.** Appl. Phys. Lett., 82: 3776-3778

Geyer, W. *et al.*: 2001. **Electron induced chemical nanolithography with self-assembled monolayers.** J. Vac. Sci. Technol., B 19: 2732-2735

Ulrich Heinzmann

1975: PhD in Physics and habilitation (1980), University of Münster, Germany
1981-1984: Head of a research group (C3), Fritz-Haber-Institute of the Max Planck Society, Berlin, Germany
Since 1984: Professor for Molecular and Surface Physics, Physics Faculty, Bielefeld University, Germany
Since 2002: Chairman of DFG SFB 613 (Collaborative Research Center)
Since 2004: Founding member of BINAS, Bielefeld University, Germany

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Selected publications

Wieland, M. *et al.*: 2005. **Towards time-resolved soft x-ray microscopy using pulsed fs-high-harmonic radiation.** Ultramicroscopy, 102: 93-100

Goulielmakis, E. *et al.*: 2004. **Direct measurement of Light Waves.** Science, 305: 1267-1269

Lischke, T. *et al.*: 2004. **Circular dichroism in valence photoelectron spectroscopy of free unoriented chiral molecules: Camphor and bromocamphor.** Phys. Rev., A 70: 022507

Brechling, A. *et al.*: 2004. **Structural organization of DMPC lipid layers on chemically micropatterned self assembled monolayers as biomimetic systems.** J. Biotechnol., 112: 115-124

Hütten, A. *et al.*: 2004. **New magnetic nanoparticles for biotechnology.** J. Biotechnol., 112: 47-63

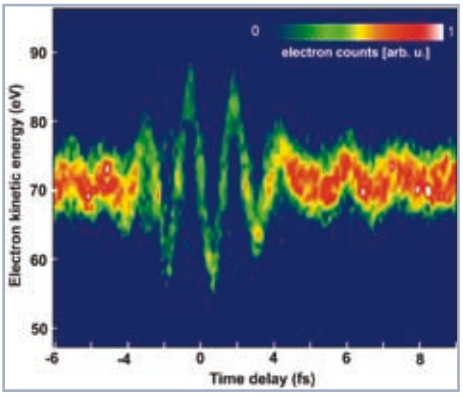
Siffalovic, P. *et al.*: 2004. **Large-scale homogeneous molecular templates for femtosecond time-resolved studies of the guest-host interaction.** J. Biotechnol., 112: 139-149

Kienberger, R. *et al.*: 2004. **Atomic transient recorder.** Nature, 427: 817-821

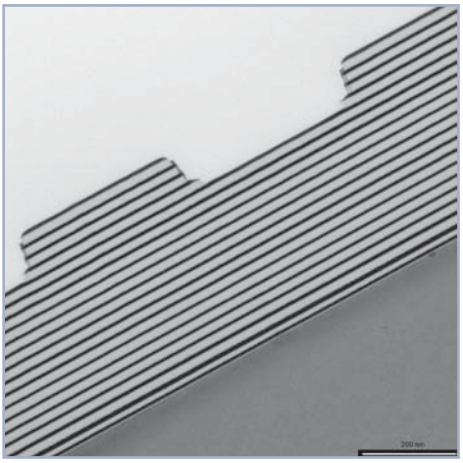
Nanotechnology, x-ray physics, atto-/femtosecond spectroscopy, electron microscopy

Previous and Current Research

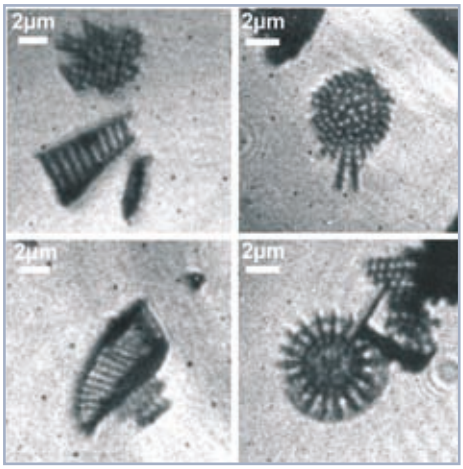
In the last two decades the research interests of the chair have developed from basic research in molecular and surface physics, such as angle- and spin-resolved photoemission spectroscopy, circular dichroism on chiral molecules and molecule-surface interaction towards applications in nanotechnology and nanobiotechnology. Ultra-thin nanometer layer deposition techniques and related analysis methods have been developed towards EUVL (extreme ultraviolet lithography) and x-ray optics for attosecond time resolved spectroscopy. The application of soft x-ray radiation such as scattering, diffraction and imaging techniques as well as of electron microscopy (TEM, SEM, STM and PEEM) on organic and bio-organic systems has come to play an increasingly important role in the research activities of the group over the past few years. Two projects in the Collaborative Research Center SFB 613 'Physics of Single Molecule Processes and Molecular Recognition in Organic Systems' have been established; these work with soft x-rays and use them to study the dynamics of molecular conformation in organic and bio-organic molecular systems, time-resolved.



The world fastest-streaking camera: Direct observation of a 4 Femtosecond short light pulse by use of x-ray pulses of 250 Attoseconds duration via the photoelectron energy distribution within the light field oscillation (Goulielmakis, E., *et al.*: 2004).



Cross-section of a nanometer-multilayer x-ray mirror by means of transmission electron microscopy (TEM).



Soft x-ray microscopy of diatom samples with a resolution of 200 nm by means of a pulsed laser-based coherent table-top radiation source (Wieland, M., *et al.:* 2005).

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Ultrafast dynamics on the nanoscale

Previous and Current Research

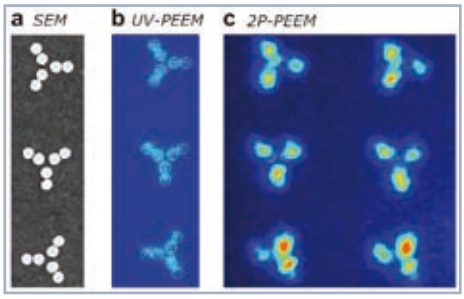
Recent developments in laser technology provide means to investigate ultrafast phenomena directly in the time-domain even with sub-femtosecond time resolution. During the last decade we have used ultrafast laser spectroscopy to study electron dynamics at interfaces in particular emphasizing electron dynamics in supported metal nanoparticles and photoinduced ultrafast transport phenomena. The ultrafast electron dynamics at nanostructured surfaces is uncovered by time-resolved laser spectroscopy combined with surface physics techniques like photoemission spectroscopy or scanning tunneling microscopy.

Photocurrent spectroscopy reveals transport and relaxation dynamics in metal-insulator-metal junctions far from equilibrium. At present, we extend the latter experiments on photoinduced charge transfer towards metal-molecule-metal junctions. Using properly anchored molecules, the photocurrent is dominated by the intramolecular charge transport. Time-resolved photocurrent spectroscopy then provides information on excited electron transfer through the molecule. Even more fascinating is the prospect to use the electric field of the laser pulse to control the photocurrent through the molecular junction.

An additional area of research is ultrafast nanooptics. The combination of ultrafast laser spectroscopy, i.e. the illumination using broadband coherent light sources and near-field optics, has recently opened a new realm for nonlinear optics on the nanoscale. We have shown that adaptive pulse shaping provides means to control simultaneously the spatial and temporal evolution of the optical near-field distribution. Thus, adaptive optics allows manipulating and steering the optical excitation in complex nanostructures, such as for example supramolecular aggregates, or ensembles of qubits.

Future Projects and Aims

The future projects will be dedicated to coherent control of electron dynamics at interfaces and in nanostructures. After its demonstration, coherent control of molecular motion or chemical reactions using shaped ultrashort laser pulses has evolved into an active field of research. In contrast, the control of electronic motion is still rather limited because of the fast dephasing and short relaxation times of electronic excitations. Carrier envelope phase stabilized few femtosecond laser pulses and attosecond laser pulses now provide sufficient temporal resolution to study and control electron motion and, thus, open a new field for research and applications.



a) Scanning electron microscopy image, b) one-photon photoemission image (UV excitation with He arc lamp) and c) two-photon photoemission image (fs-laser excitation, 795 nm) of a planar Ag nanostructure (ca. 700 nm diameter) used in experiments demonstrating adaptive optical-near-field control.

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BINAS – Bielefeld Institute for Biophysics and Nanoscience
Thin Films and Nanostructures

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Selected publications

Van Waeyenberge, B. *et al*.: 2006. **Magnetic vortex core reversal by excitation with short bursts of an alternating field.** Nature, 444: 461

Kou, X. *et al.*: 2006. **Temperature dependence of the resistance of magnetic tunnel junctions with MgO barrier.** Appl. Phys. Lett., 88: 212115

Reiss, G. and Meyners, D.: 2006. **Reliablity of field programmable magnetic logic gate arrays.** Appl.Phys. Lett., 88: 043505

Reiss, G. and Hütten, A.: 2005. **Magnetic Nanoparticles - Applications beyond datastorage.** Nature Materials - News and Views, 4: 725

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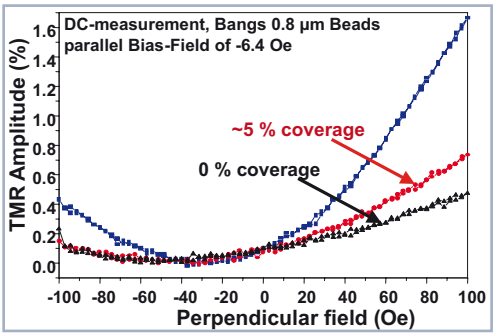
Magnetism on the nanoscale: from spinning electrons to smart applications

Previous and Current Research

The research activities of the Group Thin Films and Nanostructures can be categorized in four different fields: (1) Materials science and characterization of magnetic thin films and the use of these structures in optimized spinelectronic devices. (2) Creation of nano-scale structures by top-down (lithography) and bottom-up (chemical thermolysis of metal-organic precursors) processes. (3) Development of biosensors and on-chip manipulation systems. (4) Computer simulation of magnetic structures to explain and tailor their properties. Our interest in magnetic thin films is driven by the investigation of magnetic tunnel junctions. These structures consist of two ferromagnetic metal electrodes separated by a very thin insulator working as a barrier for the tunneling electrons. These devices exhibit the so-called tunnel magneto resistance (TMR). Their resistance depends on the relative orientation of the magnetization of the electrodes. New electrode and tunnel barrier materials (e.g., Heusler compounds and MgO) are under current investigation to tailor their properties for applications such as non-volatile random access memory, biosensors and programmable magnetic logic circuits.
Self-organized arrays of magnetic nanoparticles as well as single particles with functionalized surfaces are very interesting for technological applications like high density data storage and as magnetic markers in biological systems for detection and manipulation of attached molecules (lab-on-a-chip). Our work also includes the preparation, the characterization and the exploration of fundamental properties of thin film stacks and magnetic nanoparticles.

Future Projects and Aims

Goals of our future research are the investigation of current-induced-magnetization-switching and coherent tunneling in MgO based magnetic tunnel junctions, spin dynamics in magnetic thin films and nanostructures and the implementation of highly spin-polarized electrode materials in magnetoelectronic devices. Furthermore, we will focus on computer simulation supported development of highly-sensitive magnetoresistive sensor arrays and magnetic logic gates. Last but not least, the preparation and characterization of core-shell nanoparticles (e.g., Co core / Au shell) with outstanding magnetic and surface chemical properties tailored with respect to the specific application will be an important issue of our work in the next years.



The resistance (TMR) signal measured during applying a magnetic field perpendicular to a biosensor surface for different coverages with DNA molecules.

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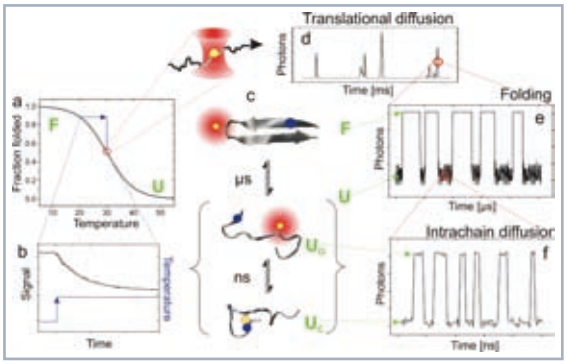
Probing fast folding dynamcis by PET-FCS

Previous and Current Research

The research interests and scientific goals of the group are based on the refined understanding of the photophysics of organic fluorophores. This deep understanding allows us to develop new and highly efficient fluorescent probes, molecular switches, and sensors for *in vitro* as well as *in vivo* applications. Besides this rather chemical and photophysical background our interests focus on the development of new optical techniques to study individual or few biomolecules, molecular assemblies, and protein machineries under natural conditions. Likewise, the group develops new probes for the early-stage detection of tumors or antibiotic resistant bacteria. As an interdisciplinary working group between physics, chemistry, biology, and medicine we are highly interested in successful collaborations with colleagues from other disciplines.

One current highlight represents the development of a new technique to study fast protein folding and conformational dynamics of biomolecules under equilibrium conditions with high temporal and spatial resolution at the single-molecule level. The technique is based on efficient fluorescence quenching of an excited fluorophore upon contact formation with the amino acid tryptophan *via* photoinduced electron transfer (PET) in combination with fluorescence correlation spectroscopy (FCS). Therefore, the technique is called PET-FCS. PET-FCS emerges as a unique method to study the earliest events of protein folding with single-molecule sensitivity, under equilibrium conditions, and with nanosecond time resolution. The technique complements state-of-the-art rapid perturbation techniques currently applied to study fast folding phenomena. In contrast to rapid perturbation, PET-FCS allows to study sub-ms folding kinetics and at the same time to monitor dynamics of intrachain diffusion, an important parameter to assess conformational flexibility within unfolded polypeptides. The method is generally applicable by site-specific introduction of Trp residues and oxazine fluorophores at tailored positions within polypeptide chains. We have recently shown that folding dynamics of a 20-residue mini-protein can be studied by fluorophore/Trp quenching where the fold remained essentially unperturbed from fluorescence modification. Meanwhile we could demonstrate that despite significant destabilization of the fold (due to the inherently low stability of isolated β-hairpins) probe-induced perturbation can be quantitatively assessed such that observed folding dynamics yield valuable information about the molecular system of interest. Understanding of the mechanisms of protein folding requires a detailed elucidation of underlying kinetic events approached by complementary theoretical and experimental techniques. In this regard, we anticipate the method PET-FCS to add a new piece to the puzzle of protein folding.



Principle of studying fast folding dynamics by PET-FCS and comparison with current techniques. Site-specific fluorescence modification allows fast folding dynamics to be probed from freely diffusing proteins at the single-molecule level in thermodynamic equilibrium. The fluorophore (red) attached to the polypeptide isselectively quenched at van der Waals contact with a Trp residue (blue) present in the sequence.

Selected publications

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Neuweiler, H. and Sauer, M.: 2005. **Exploring life by single-molecule fluorescence spectroscopy.** Anal. Chem., 77: 179A-185A

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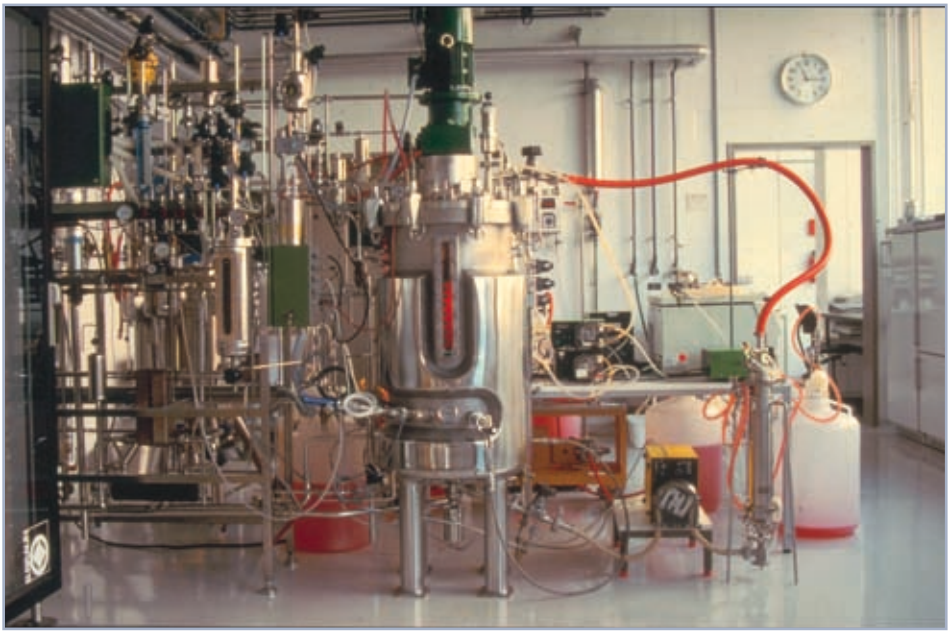
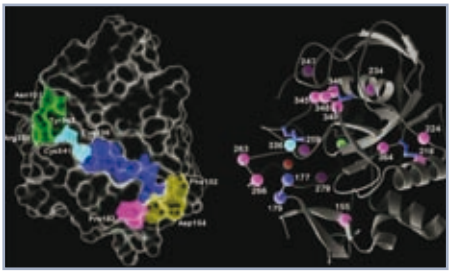
Biochemistry as one of the central disciplines of modern life sciences focuses on a detailed understanding of biological processes at the molecular level, while biotechnology aims at the application of biological processes on a technical level with numerous benefits for medical sciences, medicinal chemistry, pharmaceutical production and other therapeutic issues like stem cell therapy. This is intimately connected both with biochemical research and biochemical engineering.

Biochemical research at BioChemTech of the CeBiTec includes scientific projects from the center of biochemistry, e.g. on structure and function of proteins (with special emphasis on membrane proteins), lipids (membrane trafficking and fusion) and carbohydrates (heparan sulfate proteoglycans as regulators of signal transduction). Furthermore, biophysical chemistry, structural biochemistry, chemical biology and mass spectrometry introduce technological platforms to the BioChemTech. The activities in the area of biotechnology at BioChemTech comprise molecular, cellular, and bioprocess engineering - in particular, genetic engineering of recombinant proteins and plasmid DNA for medical



purposes, including bioprocess development, large-scale production, downstream processing, and biocatalysis.

BioChemTech, the Institute of Biochemistry and Bioengineering has been founded in order to complement the existing activities at CeBiTec. BioChemTech has many interfaces for joint activities with scientists both from inside and outside the CeBiTec. Twelve research groups together founded BioChemTech in 2006.



Molecular basis of a fatal disease. Sulfatases contain formylglycine. This unique amino acid is post-translationally generated through oxidation of a specific cysteine by the formylglycine-generating enzyme (FGE). The 3D structure of FGE was recently solved in collaboration with Markus Rudolph (Strukturbiologie, Göttingen, Germany) and is shown in surface (left) and ribbon presentation (right). In patients with multiple sulfatase deficiency, a fatal inherited disease, mutations (colored spheres) were found, leading to structural destabilization (pink), inhibition of substrate binding (blue) or block of enzyme activity (cyan) (according to Dierks, T., *et al*.: 2005. Cell, 121: 541-552).

Contributing Units

Biochemistry
Prof. Dr. Thomas Dierks

Cellular Biochemistry
Prof. Dr. Gabriele Fischer von Mollard

Fermentation Engineering
Prof. Dr. Erwin Flaschel

Biophysical Chemistry
Prof. Dr. Joachim Heberle

Organic Chemistry
Prof. Dr. Jochen Mattay

Cell Culture Technology
Prof. Dr. Thomas Noll

Cellular Genetics
Prof. Dr. Hermann Ragg

Bioorganic Chemistry - Chemical Biology
Prof. Dr. Norbert Sewald

Structural Biochemistry
Juniorprof. Dr. Hartmut Niemann

Algae Biotechnology
PD Dr. Olaf Kruse

Bioorganic Chemistry
PD Dr. Norbert Schaschke

Biophysical Chemistry
Dr. Tilman Kottke

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Selected publications

LAMANNA, W.C. *et al.*: 2006. Heparan sulphate 6-*O*-endosulphatases – discrete *in vivo* activities and functional cooperativity. Biochem. J., 400: 63-73

ROESER, D. *et al.*: 2006. A general binding mechanism for all human sulfatases by the formylglycine generating enzyme. Proc. Natl. Acad. Sci. U.S.A., 103: 81-86

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PREUSSER-KUNZE, A. *et al.*: 2005. Molecular characterization of the human C_α-formylglycine generating enzyme. J. Biol. Chem., 280: 14900-14910

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Biogenesis and multi-faceted functions of sulfatases in health and disease

Previous and Current Research

Our research is directed towards sulfatases, enzymes with considerable medical impact. Biochemical, structural and cell biological investigations are performed including the generation and analysis of mouse models. Six sulfatase deficiencies lead to fatal disorders of the lysosomes with failure to catabolize sulfated biomolecules such as glycosaminoglycans or glycolipids. Systematic remedy has been made possible by administration of recombinant sulfatases (enzyme replacement therapy). Recent clinical trials were successful. Together with an industrial partner we are developing cell lines for efficient production of newly discovered sulfatases for biochemical characterization and eventual medical application. To this end, co-expression with the so-called formylglycine generating enzyme (FGE) improved the specific activity of the produced sulfatases up to 50-fold. We identified FGE in 2003, prompted by our discovery that all sulfatases carry a unique amino acid, C_α-formylglycine (FGly), which is essential for their catalytic function. FGE post-translationally generates this FGly by oxidation of a specific cysteine according to an unusual oxygenase mechanism. The 3D structure of FGE, determined recently, defines a new protein family that is conserved in evolution.

Future Projects and Aims

Heparan sulfate proteoglycans are of prime interest due to their function as signaling regulators at the cell surface that are specifically degraded or modified by several sulfatases. Within the glycan chains, specific sulfation patterns determine the binding, activation or gradient formation of multiple growth factors, morphogens etc. and thereby trigger signaling pathways during development. Two unique sulfatases, Sulf1 and Sulf2, act as the major editing enzymes of these sulfation patterns, as evidenced by analysis of our Sulf1/2 knock-out mice (Fig. 1). Sulf1 has been described as a tumor suppressor; it stimulates Wnt, but reduces FGF signaling (Fig. 2). We study the biological and molecular phenotype of the mice and the impact of the Sulfs on many cell biological and biochemical aspects of tumorigenesis, differentiation, apoptosis, immune response, wound healing etc. *in vivo* and *in vitro*.

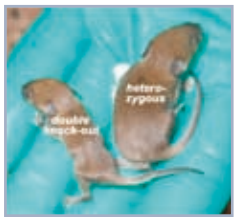

Fig. 1: Double knock-out mice deficient in both Sulf1 and Sulf2 show high embryonic lethality. Survivors are much smaller and have a short life span.

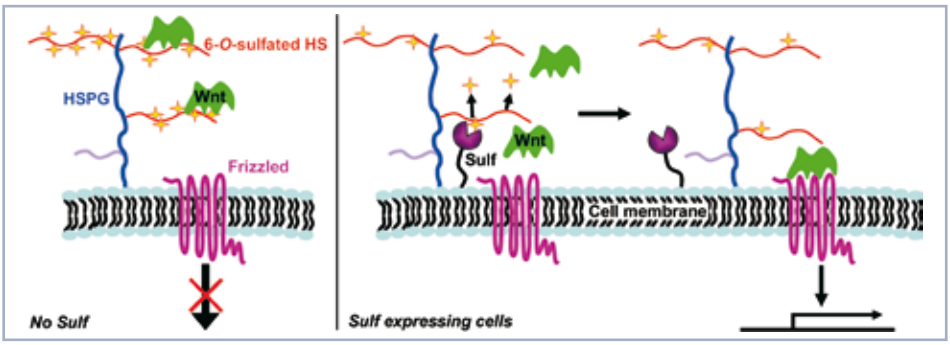

Fig. 2: Heparan sulfate proteoglycans (HSPG) at the surface of animal cells firmly associate with multiple signaling molecules such as Wnt, an important regulator of embryonic development. By releasing specific sulfate groups, Sulf1 enables Wnt binding to its cognate receptor (frizzled), signal transduction to the nucleus and activation of Wnt target genes (according to Lamanna, W.C., *et al.*: 2007, in press).

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2005: Professor for Biochemistry, Department of Chemistry, Bielefeld University, Germany

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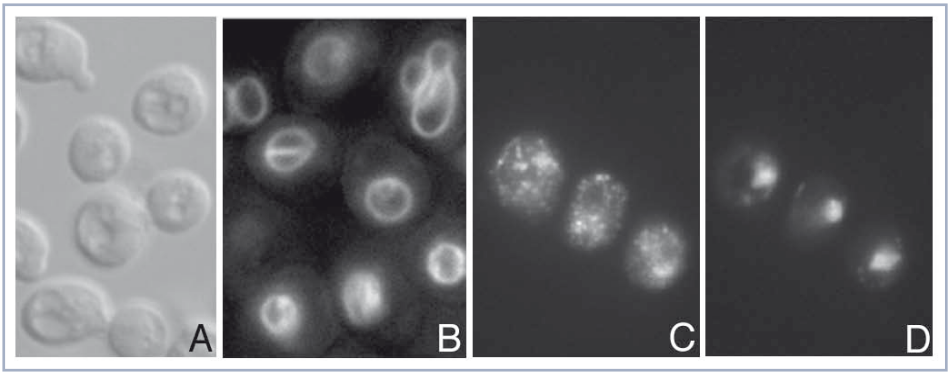
Molecular mechanisms of intracellular membrane traffic

Previous and Current Research

Eukaryotic cells are characterized by specialized compartments, which are enclosed by membranes. Molecular mechanisms of intracellular membrane traffic *via* transport vesicles are analyzed. Research concentrates on the family of SNARE proteins, which are required for recognition between transport vesicle and target membrane as well as for subsequent membrane fusion. Proteins interacting with SNAREs are studied, which direct transport and subcellular distribution of SNAREs. A second focus is transport between the plasma membrane, Golgi, endosomes and lysosomes. Such endosomal pathways are essential for regulation of signal transduction in survival, growth and development of cells, for nutrient uptake, for immune defense and for entry of pathogens. The endosomal system as well as the proteins involved is conserved in evolution allowing us to use the baker's yeast *Saccharomyces cerevisiae* as a model system for mammalian cell function. Yeast is a powerful model system because a combination of genetics, biochemistry and fluorescence microscopy can be used. In addition, mammalian cells and knock out mice are studied. Mice deficient for different SNAREs were generated. Cells derived from these knock out mice are analyzed for subcellular distribution of organelles and proteins as well as for transport processes by biochemical and microscopical methods.

Future Projects and Aims

It is planned to analyze the spatial regulation of signal transduction. Redistribution of growth factor receptors between cell surface and endosomes can change signaling due to exposure to different components of the signal transduction cascade. Mice deficient for different SNAREs will be used to investigate the role of the endosomal system in neuronal survival and development. This may provide new insights into neurodegenerative diseases.



Microscopical images of yeast cells. A: Difference interference contrast microscopy with vacuoles visible as dimples. B: Vacuoles stained with the fluorescent membrane dye FM4-64. C: Immunofluorescence with antibodies directed against the SNARE Vti1p found in Golgi and endosomes. D: Nuclei stained with the DNA dye DAPI.

Selected publications

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White Biotechnology: cultivation of microorganisms, downstream processing, and biochemical reaction engineering

Fermentation processes

The cultivation of microbial organisms by means of high cell density fermentation and integrated processes are of primary interest. Research and development are dealing with different classes of biotechnological products – proteins, oligo- and polysaccharides, respectively, as well as plasmid DNA for gene therapy and genetic vaccination. *Eschericha coli, Klebsiella planticola*, and other bacteria are those organisms applied most frequently. In addition, the social amoeba *Dictyostelium discoideum* has been studied with respect to the expression of heterologous proteins, and *Euglena gracilis* under heterotrophic conditions for the purpose of producing its storage polysaccharide paramylon. The degradation of oil and the production of biosurfactants are actual topics as well.

Downstream processing

The same products as cited above are in the focus of research in downstream processing. The main aim with respect to proteins is the improvement of protein purification by means of genetic engineering methods. Thus, target proteins are fused with affinity tags, which are able to yield affinity interactions. A novel affinity tag has been developed which is of particular interest for applications in extraction as well as precipitation processes. By coupling of the tag with the green fluorescent protein (GFP) from *Aequorea victoria* a model system has been worked out, by means of which the location of the target protein and its state can be followed by visual inspection. Another central topic of research is the secretion of proteins into the medium of Gram-negative bacteria. The secretion into the medium has been achieved by means of the expression of the *kil* gene under control of stationary phase promoters. Actual research is directed to understanding of the regulation of the secretion pathway. In addition, natural stationary phase promoters as well as libraries of synthetic ones are studied intensively. In connection with tools from bioinformatics such characteristics as the induction time and the height of expression shall be correlated with the structure of the promoters. In this case the marker GFP is used, too.

Biocatalysis and enzyme engineering

Main projects worked on so far are to be found in applications for the food and pharmaceutical industry. In the area of the enzymatic stereospecific C-C coupling the substrates of the reaction had at first to be synthesized. In most cases this had to be achieved by means of enzymatic reactions as well. Thus, a novel enzyme can now be supplied for the production of a central building block of aldolases – dihydroxyacetone phosphate. Main reactions were studied on a scale of 2 liter in enzyme membrane reactors in order to be able to study the recycling of the enzymatic activity under realistic conditions. Reaction systems with several fluid phases are of particular interest. In consequence, fixed bed reactors of immobilized enzymes fed with two liquid phases have been studied.

Particular current activities

Questions with respect to the differences on all molecular levels of closely related bacterial strains and after separate evolution have been addressed. Experiments under well defined operating conditions are the key for studies of the cellular transcriptome, proteome, and metabolome. The differences found may change the strategy of host selection.

In situ microscopy is used to count cells and at the same time determine their viability. For this purpose a bright field microscopic probe has been equipped with a dark field illumination. Support vector machines are used to yield both cell counting and viability analysis online for yeast actually.

Selected publications

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Risse, J.M. *et al.*: 2005. Production of N-acetyl-phosphinothricin: A substance used for inducing male sterility in transgenic plants. Eng. Life. Sci., 5: 38-45

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Beshay, U. *et al.*: 2003. Analysis of the behaviour of *Dictyostelium discoideum* in immobilized state by means of continuous cultivation. Bioproc. Biosyst. Eng., 26: 117-122

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The molecular machinery of (membrane) protein action

Previous and Current Research

The cell membrane is the target of more than 60 % of all pharmaceutical drugs. It is of fundamental importance to understand the functional properties of membrane proteins at the atomic level. Many of these molecular machines are triggered by light (photosynthetic and retinal proteins) or by electrons (cytochrome c and its oxidase) and have been intensively studied to resolve the dynamics on a physico-chemical basis. Structural changes of the protein backbone and the co-factor, proton transfer or changes in H-bonding were traced with a time-resolution of 5 µs. A more recent branch comprises the elucidation of the mechanism of blue-light receptors that are ubiquitously distributed among all kingdoms of life. This work is done in collaboration with the Helmholtz-Hochschul-Nachwuchsgruppe of Dr. Kottke.

We are employing and developing vibrational spectroscopy (FTIR and resonance Raman) to study the functional dynamics of proteins with high time-resolution (Figure 1). Even monolayers of membrane proteins can be studied by surface-enhanced vibrational spectroscopy. The assignment of the difference bands to changes in vibrational modes of the corresponding chemical bonds provides a very sensitive means of detecting even minute changes during the catalytic action of the enzyme.

Future Projects and Aims

More then 20 % of the human genome encodes for membrane proteins. The membrane proteome of several model organisms will provide a wealth of new membrane proteins whose functional mechanisms remain to be resolved. Based on our established expertise, we will set out to study the functional mechanisms of other membrane proteins and their interaction with their cognate partner proteins. As a long term goal, we are aiming at the elucidation of the reaction mechanism of voltage-gated ion channels. Beyond their biomedical relevance, membrane proteins are central in bioenergetic processes like photosynthesis and respiration. We will continue in the development of a semi-artificial device for (bio-)hydrogen production utilizing photosynthetic water oxidation. With this approach, the energy of the sunlight is converted into the generation of H_2 without the emission of CO_2.

Funding

Research is supported by grants from the Ministry of Education and Research and the German Research Foundation (DFG) with projects in the SFB 663 as well as the Forschergruppen 450 and 526. We are involved in a virtual institute generated by the Helmholtz-Gemeinschaft (VH-VI-013).

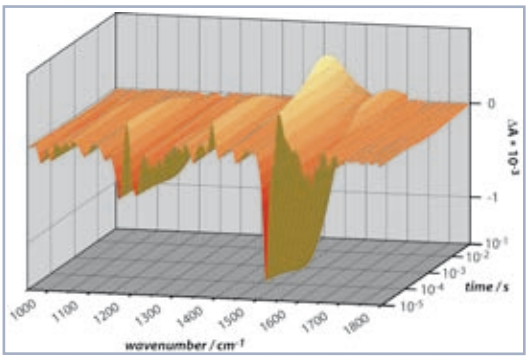

Fig. 1: Time-resolved FT-IR spectroscopy probes the conformational changes of the light-driven halogen pump halorhodopsin.

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Organic and physicalorganic chemistry, supramolecular chemistry, photochemistry, and mass spectrometry

Previous and Current Research

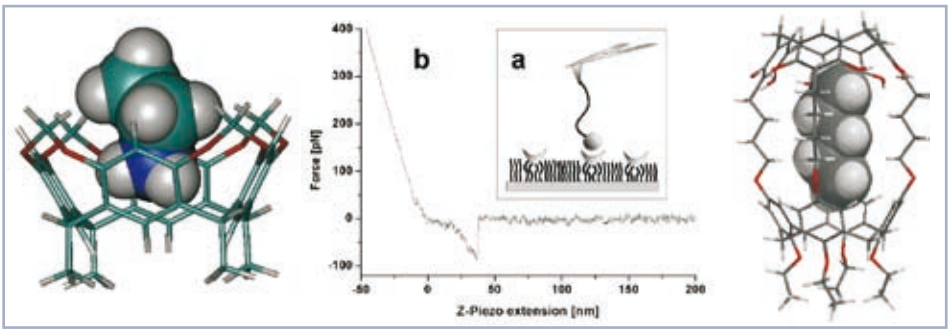
Our research program covers aspects of small organic molecules, higher noncovalent aggregates at the nanoscale, and large entities at the mesoscopic scale. We are especially interested in evaluating the factors which determine the reactivity of molecules and which control their self association to higher aggregates such as molecular capsules, self assembled monolayers, and LB-films. In this context various modern analytical methods are used to elucidate structure and reactivity of these molecular entities: NMR, MS, UV/Vis absorption, Fluorescence and Phosphorescence, Laser-flash techniques (in collaboration), AFM- and other surface techniques (in collaboration), Matrix Isolation (in collaboration). Especially Mass Spectrometry has been shown to be unique in getting detailed information about structure and function of molecular entities at the nanoscale.

Future Projects and Aims

Future projects aim at the design of photoswitchable host-guest systems derived from calixarenes, molecular tweezers of the Hamilton-type, and peptides. Molecular capsules which may be used for transport of active substances e.g. through membranes will be studied to complement our activities focused on the synthesis of photoswitchable ion channels. The tools of Organic Photochemistry will also be applied for developing photomodifiable surfaces and photoswitchable dyes for high resolution Fluorescence-Tracking and -Imaging (BMBF-Forscherverbund).

Cooperations

Bielefeld University: Experimental Biophysics and Applied Nanoscience (D. Anselmetti), Applied Laser Physics and Laser Spectroscopy (M. Sauer), Molecular and Surface Physics (U. Heinzmann), Physics of Supramolecular Systems (A. Gölzhäuser), Bioorganic Chemistry (N. Sewald), Theoretical Chemistry (U. Manthe and W.W. Schoeller, new address: University of California, Riverside, U.S.A.). - University of Paderborn: Time-resolved Light Scattering. - University of Fribourg, Switzerland: Matrix Isolation and Quantum Chemistry (T. Bally). - Osaka University, Japan: Chiral Photochemistry (Y. Inoue). - University of Ulm, Germany: LB-films and Giant Molecular Containers (D. Volkmer). - University 'La Sapienza', Rome, Italy: Mass Spectrometry (M. Speranza). - University of Kielce, Poland: Calixarene Chemistry (W. Iwanek).



Host-guest complex between a cavitand and ethyl ammonium (left), force-distance curve and force histogram from an AFM experiment at single molecule level (center), and covalent molecular capsule with a nonsymmetric cavity containing *n*-pentane as guest (right).

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Cell Culture Technology: process development for protein production and cellular therapy

Previous and Current Research

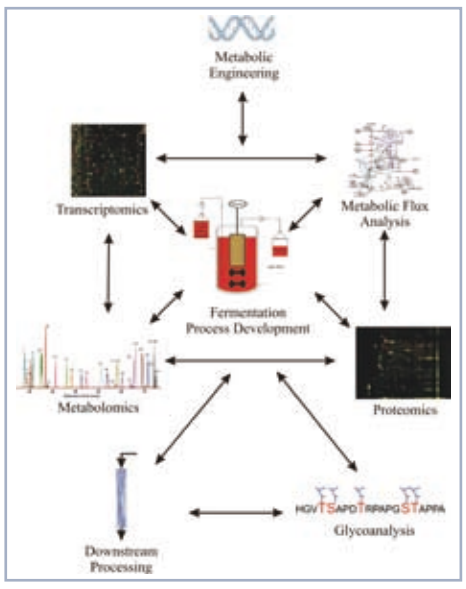
Mammalian cells are of increasing interest for the production of therapeutic proteins and vaccines especially if correct post-translational modifications are required. In close collaboration with scientific and industrial partners we have developed optimized fermentation processes for the production of several recombinant proteins including a metabolically optimized perfusion process which results in an improved central and energy metabolism and in a 3fold increase in cell specific productivity.

Since a few years we have started to combine classical approaches for process development with techniques from functional genomics like metabolic flux analysis, differential proteomics and intracellular metabolomics. Although most of those techniques which are well established for microbial systems first had to be adapted to mammalian cells or in some cases even newly developed, first results have shown the potential of this approach for an accelerated and more rational process development.

A second focus of our research is on the development of optimized bioreactors and cultivation processes for the *ex vivo* expansion of somatic human cells for cellular therapy. Our main target have been hematopoietic stem cells from umbilical cord blood but very recently in cooperation with the University of Witten-Herdecke we have started to work on adult stem cells from periodontal tissue. Several miniaturized and parallelized bioreactors (in some cases including online process control) have been successfully developed.

Future Projects and Aims

Our aim is to further develop and combine the functional genomics tools mentioned above to get a quantitative understanding of the cellular reactions to cultivation conditions in a laboratory and in an industrial scale. The latter case first requires the development of valid scale down models to simulate the specific properties of a 10,000 liter stirred vessel bioreactor in a lab scale. We hope and expect that these data will enable us to identify potential targets for genetic optimization of the production cell lines, for medium and bioprocess optimization and therefore contribute to a rational, rapid and more efficient fermentation process development.



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Selected publications

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The role of inhibitors in the maintenance of homeostasis and in pathophysiological processes

Previous and Current Research

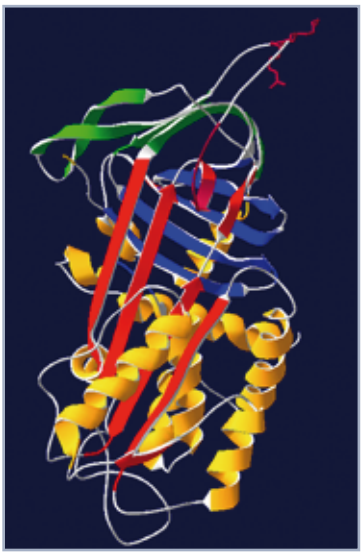
We are intrigued by the fascinating biochemistry and genetics of the serpins (serine protease inhibitors), a family of proteins that is characterized by an unusual plasticity of structural and functional properties. Members of the serpin family may exert such divergent functions as protease inhibition, assisting in protein folding, and chromatin condensation, often involving large-scale conformational changes.

We have identified and characterized some serpins that are potent inhibitors of proprotein convertases, a class of processing enzymes responsible for maturation of many hormones, neuropeptides and other cellular proteins, but also involved in far-spread pathologies such as cancer, arteriosclerosis and dementia. In addition, proprotein convertases are associated with the propagation of many pathogens, like HIV, *Bacillus anthracis* or Ebola virus. Currently, we are investigating the molecular basis of serpin/proprotein convertase interaction aimed at identifying the molecular basis that dictates the recognition of specific enzyme/inhibitor pairs.

A special interest of our research relates to serpins from *Drosophila melanogaster*, an animal that has often proven as a front runner for solving important biological questions. Our aim is to delineate the biochemical and physiological functions of serpins from this model organism.

Future Projects and Aims

The focus of our research is the biochemistry, genetics and physiology of serpins from man, *Drosophila melanogaster* and other metazoans. It is planned to develop novel methods that allow the elucidation of the function of serpins on a genome-scale level. Furthermore, we are interested in analyzing the interaction of serpins and proprotein convertase-like enzymes and to investigate the (patho)-physiological conditions that may interfere with the protease/inhibitor balance in a wide range of infectious diseases and other pathologies, and that ultimately may contribute to the development of agents for pharmacological intervention. Finally, we are interested in getting more insight into the molecular evolution of the architecture of serpin genes from metazoans that is characterized by an unusual divergence of exon/intron structures.



Model of a serpin molecule. Structural plasticity and functional diversity provide the molecular basis for a large variety of functions associated with these proteins.

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Bioorganic Chemistry - Chemical Biology

Previous and Current Research

Organic chemistry on the borderline to biology and medical sciences:

- Chiral reagents and catalysts
- Isolation and total synthesis of natural products
- Molecular tools for life science research
- Peptide-protein interactions, peptide-DNA interactions
- Conformational analysis using NMR and MD

Biologically Active Peptides

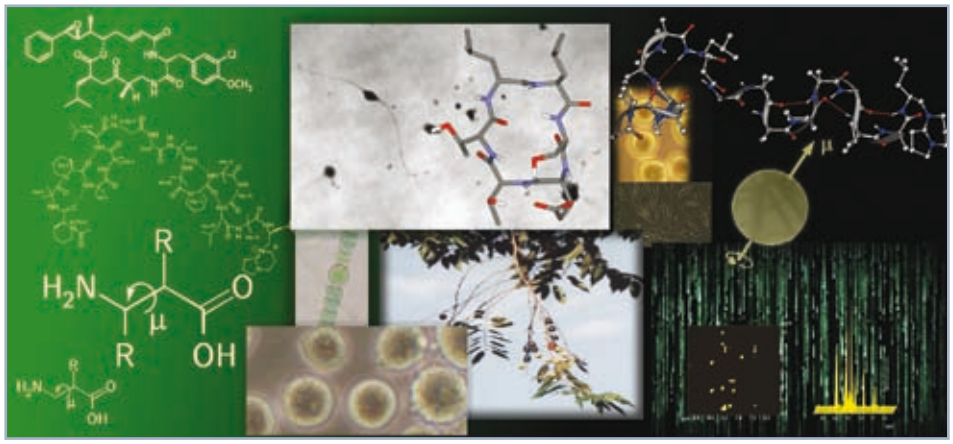
Peptides and proteins are naturally occurring biomolecules, composed of amino acids. In many cases the interaction between proteins, which is crucial for physiological events, can be influenced by peptides with a well-defined three-dimensional structure. The combination of NMR spectroscopy and molecular dynamics simulations provides a powerful tool for the elucidation of the solution structure of peptides and, hence, for the investigation of peptide-protein interactions. This methodology is complemented by binding studies with surface plasmon resonance enabling real-time monitoring of biomolecular binding events. Certain peptides may also be used for the selective delivery of toxic substances to tumor cells in order to reduce side effects in tumor therapy.

Molecular Tools for Life Science Research

The post-genome era will increasingly focus on proteins as the main effector molecules in biological systems. The analysis of the proteome, the entirety of all proteins expressed by a cell under certain conditions, is a new and very challenging task. Tailor-made chemical probes, obtained by synthesis, significantly contribute to the advanced methods of proteome analysis.

Future Projects and Aims

- The role of chemistry in systems biology
- Synthetic biology



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Selected publications

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Protein X-ray crystallography

Previous and Current Research

Experimental structure determination is an essential contribution to a thorough functional understanding of biological macromolecules at the molecular level. For most proteins and protein complexes X-ray crystallography is the method of choice to obtain structures. Crystallography can provide information both about the arrangement of proteins in large assemblies and about individual amino acids and their function, e.g. in ligand binding or catalysis. We have used crystallography to structurally characterize the protein dynamin and, more recently, virulence factors of pathogenic bacteria.

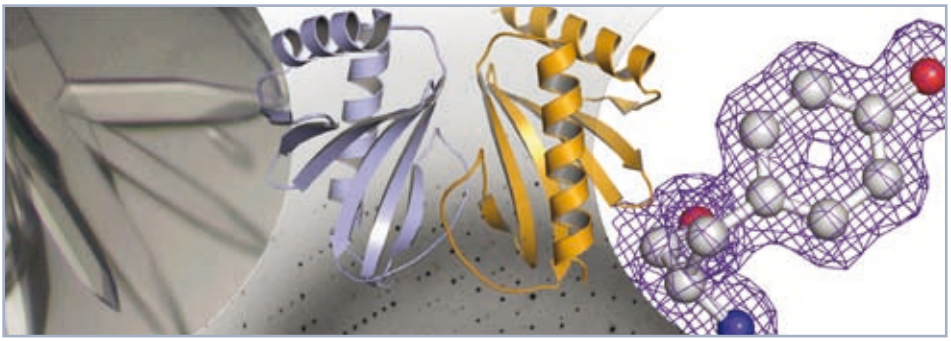
Virulence factors are proteins produced by pathogens to specifically influence their host to their own benefit. They are essential to cause disease and usually not found in related apathogenic bacterial strains. Often, virulence factors interfere with and abuse existing signaling pathways of the host through direct interaction with host cell components. Structures of virulence factors in complex with their target proteins further our understanding of infection processes and of the endogenous cellular processes influenced by the pathogen.

Among the virulence factors that we investigate is the protein InlB. *Listeria monocytogenes*, the causative agent of human listeriosis, employs the invasin InlB to invade host cells where it is shielded from the humoral immune response. InlB functions by binding and activating the proto-oncogene Met. The receptor Met normally regulates cell growth and migration and its hyper-activation can promote cancer metastasis. A crystal structure of the Met / InlB complex will reveal molecular determinants of the interaction and of receptor activation.

Future Projects and Aims

Structural and functional characterization of proteins and protein complexes involved in

- Host-pathogen interaction
- Signal transduction



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Molecular biology research on unicellular green algae for biotechnological applications

Previous and Current Research

In current biotechnology research, micro algae play a critical role for the production of food, chemicals, and fuels. They are used as important catalysts for biodegradation approaches and their biomass is converted to pharmaceutical products.

Certain green algae, such as *C. reinhardtii* have evolved the additional ability to convert solar energy into H_2 derived from water splitting. This is of particular relevance, since the development of clean borderless fuels is of vital importance to human and environmental health and global prosperity, more than almost any single issue facing mankind today.

The solar bio-H_2 process in *C. reinhardtii* has been identified as one of the most promising sources of clean fuel for the future. The (sunlight to H_2) conversion efficiency is high (~10 %), however only for transient periods, owing to yet incompletely understood mechanisms. The H_2 production process depends on the interplay of a wide range of metabolic processes including photosynthesis, respiration and the fermentation of stored carbohydrates.

Our research is based on recently constructed high H_2 production *C. reinhardtii* mutants *Stm6* and *Stm6glc4* (Patent No. 2003903453). These mutants have conversion efficiencies of more than 2 % and gas purities which have been shown to be sufficient to power a small scale fuel cell without further purification.

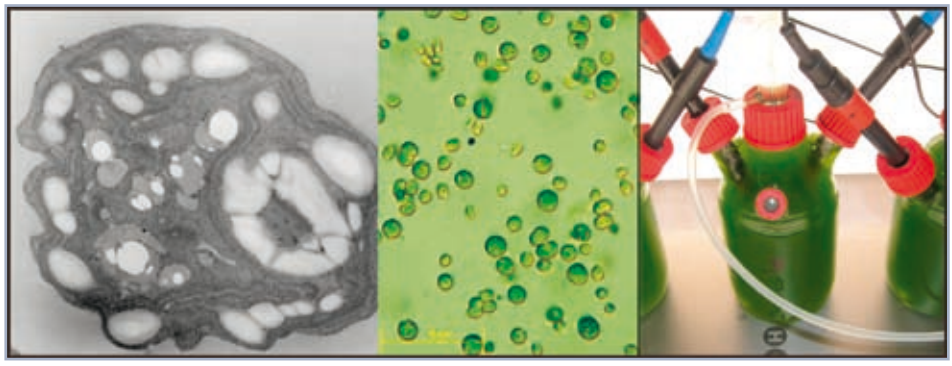
Future Projects and Aims

The aims of our projects are to improve biomass production with unicellular micro algae and to develop a competitive solar powered H_2 production system, based on engineered cells.

High H_2 production *C. reinhardtii* mutants *Stm6* and *Stm6glc4* are used for systematic analysis of solar-driven H_2 production pathways (Systems Biotechnology) and their H_2 production capacities will be further optimized through parallel biotechnology and engineering driven approaches.

The projects integrate advances based on parallel research streams being conducted in our laboratory in collaboration with partners in Australia and Germany, with the specific aim to combine solar-driven biomass and bio-H_2 production with the technical development of an economically profitable algal photo-bioreactor.

We furthermore aim to couple photo-biological H_2 production with the development of 'near market' biomass and biodiesel production systems.



The high H_2 producing *C. reinhardtii* mutant *Stm6*.

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2000-2005: Research Associate, MPI of Biochemistry, Martinsried, Germany
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Selected publications

SCHASCHKE, N. *et al.*: 2005. **Affinity chromatography of tryptases: design, synthesis and characterization of a novel matrix-bound bivalent inhibitor.** ChemBioChem., 6: 95-103

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Tailor-made synthetic inhibitors: tools for characterizing proteolytic activity

Previous and Current Research

Proteolysis is a general mechanism that regulates a variety of physiological processes. However, our knowledge of many key proteases is still limited. Bioorganic Chemistry provides molecular concepts to learn more about the individual role and redundancy of proteases in a complex physiological context. In particular, tailor-made synthetic protease inhibitors that selectively recognize and bind their target enzymes represent versatile tools for this task in different disciplines of life sciences. We have selected for our studies as targets the papain-like cysteine protease cathepsin B and the trypsin-like serine protease β-tryptase. Based on the thiol-reactive group (2*S*,3*S*)-oxirane-2,3-dicarboxylic, a probing system for the proteolytic activity of extracellular cathepsin B has been designed and synthesized (Fig. 1). Applying this probe in cooperation with research groups from immunology and cell biology, novel physiological functions of this enzyme could be identified. Furthermore, addressing simultaneously two S1 binding pockets of neighboring subunits of the tryptase tetramer with the appropriate dibasic ligand (Fig. 2), we have developed an affinity chromatographic method to discover proteolytic activity originating from β-tryptase. Additionally, we are interested in natural products with novel protease-inhibiting activities. Using material obtained by total synthesis, we were able to identify a unique protease class-spanning inhibitory profile of the sponge-derived miraziridine A.

Future Projects and Aims

We plan to extend our established synthetic strategies on cysteine as well as multimeric proteases, respectively. The platform (2*S*,3*S*)-oxirane-2,3-dicarboxylic allows to address in a simultaneous fashion both S and S' binding pockets along the active site cleft with attached peptide portions and thus should provide a general access for tools that selectively label diverse cysteine proteases. Similarly, using the concept of bivalency it should be possible to address differing spatial arrangements of S1 binding pockets of multimeric proteases.

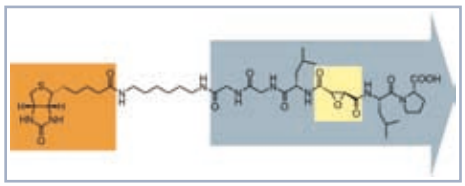

Fig. 1: Chemical structure of the cathepsin B probe. The probe head is highlighted in blue, the thiol-reactive group in yellow, and the reporter group in orange.

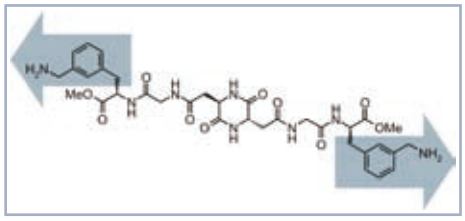

Fig. 2: Chemical structure of a bivalent ligand that recognizes β-tryptase. The S1 binding heads are highlighted in blue.

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Structure and function of biological blue light receptors

Previous and Current Research

Blue light is one of the major environmental factors governing the growth of plants and the daily 24h rhythm of many organisms. Although its effects have been studied for more than a century, only now the underlying molecular processes are being revealed. Light perception is achieved by means of sensory photoreceptors, which are proteins incorporating a chromophore as light-sensitive molecule. Most blue-light receptors use derivatives of riboflavin (vitamin B2) as chromophore. Three classes of flavin-containing receptors have been identified in the recent past: phototropins, cryptochromes and sensors of blue light using FAD (BLUF).

We are interested in the molecular mechanism of signal transfer from the chromophore to the surface of the protein. Information about the light conditions in the environment of the organism somehow needs to be converted from a localized electronic excitation to a movement of complete structural elements of the protein and to a change in interaction with signaling partners. The reaction principles behind the blue-light receptors differ from those of all other known photosensory receptors such as the retinal in our eyes.

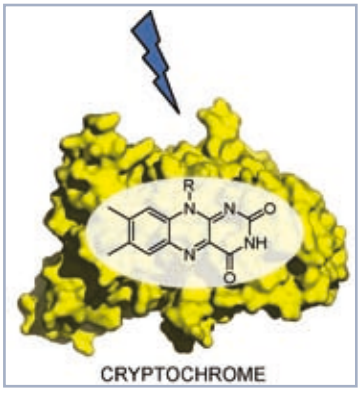
The structural changes taking place in the biomolecule are tracked using mainly a combination of Fourier transform infrared spectroscopy and resonance Raman spectroscopy. This allows us to gain a comprehensive overview of chemical processes of the light-absorbing molecule as well as responses by the protein shell. The temporal evolution of the light-driven reaction can be followed by time-resolved techniques in the time range from microseconds to minutes.

This approach enabled us to shed light on the primary light-induced processes in the plant cryptochrome 1 from *Arabidopsis*. In comparison, the effect of light on the animal cryptochrome from *Drosophila* was studied. Furthermore, we investigated the signal pathway within the light-sensitive domain of algal phototropin and the interdomain interaction.

Future Projects and Aims

It is conceivable that the revelation of the novel concepts behind the blue-light receptors gives impulses to the development of sensors or photo-switchable devices. Before, the basic working principles behind these blue-light receptors need to be understood in detail.

We will continue with our investigations focusing mainly on the cryptochromes, which are found in all kingdoms of life including us humans. The cryptochromes are still at the beginning of being characterized by biophysical techniques due to manifold problems with sample preparation. We have recently overcome these difficulties and are now in a position to gain insight into the mechanism.



Blue light induces changes in the sensory receptor cryptochrome (PDB 1U3C), regulating plant growth and setting the biological clock in plants and animals.

Selected publications

Kottke, T. *et al.*: 2006. **Blue-light-induced changes in *Arabidopsis* cryptochrome 1 probed by FTIR difference spectroscopy.** Biochemistry, 45: 2472-2479

Kottke, T. *et al.*: 2006. **The photochemistry of the light-, oxygen-, and voltage-sensitive domains in the algal blue light receptor Phot.** Biopolymers, 82: 373-378

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International NRW Graduate School in Bioinformatics and Genome Research

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Combining bioinformatics and experimental genome research in an international PhD program of excellence

The International NRW Graduate School in Bioinformatics and Genome Research is an educational institution devoted to top-level research in bioinformatics and molecular biology. The NRW Graduate School offers a fast track, high-level PhD program for students with excellent qualifications.
We believe that young scientists need to be closely integrated in interdisciplinary projects across all involved sciences to give them the vast range of experience needed for future research in the life sciences. Ideally, this involves PhD students working in pairs on closely related projects solving open problems in experimental and computational domains. To achieve this goal, we follow a thorough recruiting, selection, supervision, and evaluation process and are constantly in contact with external experts.

History

Genome research was successfully established at Bielefeld University by participating in the yeast genome project in 1990. Since then numerous bacterial genomes were sequenced at the Chair of Genetics and the CeBiTec.
Moreover, Bielefeld University established its reputation in excellent PhD education of interdisciplinary science with the establishment of the DFG Research Training Group 231 'Structure Formation Processes' in 1996. The mission of this program was to bring together mathematicians and computer scientists to work together with biologists, chemists, physicists, linguists and economists on the mathematical modeling of pattern formation processes. It has catalyzed the cooperation between mathematics, molecular biology, biochemistry, and computer science.
When bioinformatics gained momentum as a new discipline (rather than a field of interdisciplinary research), this gave rise to the DFG Research Training Group 635 'Bioinformatics', reflecting that the needs of the day were most urgently directed towards software and algorithmics to handle and interpret the upcoming large amounts of genomic data. A number of joint activities resulting from this point have turned Bielefeld University into one of the leading bioinformatics sites in Germany and beyond, as visible from the success in the DFG Bioinformatics Initiative in 2000, the endowment with the International NRW Graduate School in Bioinformatics and Genome Research in 2001 by the Ministry for Science and Research (MWF) of the State of Northrhine Westphalia (NRW), and the acquisition of funds from the IPP PHD program by the German Academic Exchange Service (DAAD) in 2004.
Today, the Center for Biotechnology serves as the hub for projects in the life sciences at Bielefeld University. Meanwhile, the faculty of the NRW Graduate School has grown to over 50 members and seven distinguished researchers of the International Faculty. Overall, 77 PhD students have been admitted to the study program, of which a third are female: 58 with scholarships from the NRW Graduate School, 13 with scholarships from the DFG, and 2 with scholarships from the DAAD, and the rest from other sources. On average 40 % of enrolled PhD students are from foreign countries.

Ensuring highest standards

The large number of peer-reviewed publications by PhD students of the NRW Graduate School shows the success of the strategy of intensive supervision and reporting combined with continuous discussion about the content and aim of research projects in a large scientific community.

You will find numerous high-ranking publications listed in this brochure written by PhD students of the NRW Graduate School.

PhD projects

The interdisciplinary PhD program combines the areas of bioinformatics and experimental genome research allowing students to acquire a PhD in either biology, chemistry or computer science. The faculty defines the three-year PhD project upon acceptance of the candidate to the NRW Graduate School. Two supervisors and the NRW Graduate School mentors support the PhD student. The PhD student lays out a project plan for the first year which is then formally approved by the application committee. Yearly written progress reports ensure that the faculty is informed of the project's progress. Great care is taken to balance time between research project and study program.

Study program

In addition to the scientific research work PhD students complete an individualized study program totaling 45 ECTS credit points, taking into account the scientific background and the subject of the doctoral thesis. The sixth semester is reserved for writing the doctoral thesis.

Progress reports

Progress reports have to be handed in by the PhD students every year to continue their fellowships. They consist of two parts, a project report and a scientific essay. The project report contains a commented version of the previous years project plan together with a plan sketching out the project details for the next year. The scientific essay consists of a summary of the scientific results obtained in the PhD project so far. It may be replaced by a publication or technical report of scientific results.

Scientific retreat

Twice a year the students and faculty of the NRW Graduate School spend two days at a conference center or hotel near Bielefeld. Students give presentations of their work after the first and the second project year. This is a good opportunity for everyone to get an overview of all scientific activities at the NRW Graduate School and to discuss findings and progress of projects.

Travel and publication funds

The NRW Graduate School welcomes the willingness of PhD students to present their results at scientific meetings. Sufficient funds are available to cover the costs of travel to international scientific conferences or the costs of publishing in international scientific journals. Moreover, short research stays of up to 3 months can also be financed.

Soft skills training

The NRW Graduate School offers soft skill training courses on demand by inviting professional lecturers. Furthermore, the University offers soft skill courses on various levels and topics that are also open to NRW Graduate School students.

Language

The language of the NRW Graduate School is English. Knowledge of German is not required for enrollment as PhD student with the University in this program. For international students funding is provided for language courses in German offered by the University‘s PunktUm program.

Selected publications

Barsch, A. *et al*.: 2006. **Metabolite profiles of nodulated alfalfa plants indicate that distinct stages of nodule organogenesis are accompanied by global physiological adaptations.** Mol. Plant-Microbe Interact., 19: 998-1013

Baumbach, J. *et al*.: 2006. **CoryneRegNet: An ontology-based data warehouse of corynebacterial transcription factors and regulatory networks.** BMC Genomics, 7: 24

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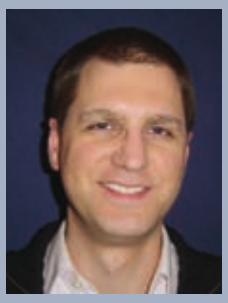
Ströher, E. and Dietz, K.J. 2006. **Concepts and approaches towards understanding the cellular redox proteome.** Plant Biology, 8: 407-418.

Voss, B. *et al*.: 2006. **Complete probabilistic analysis of RNA shapes.** BMC Biol., 4: 5

Bioinformatics Resource Facility



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Data management and data integration in the '-omics' Sciences

Previous and Current Research

Systems biology is an emerging new research field of biology, which is fostered by the availability of high-throughput technology in genome and post-genome research. Based on available genomic sequences well established techniques, e.g. for transcriptome or proteome analysis generate exponentially increasing amounts of qualitative and quantitative data. In principle, the process of data generation by such experimental techniques seems to be unlimited, but only semantic integration of these heterogeneous data sets allows for comprehensive discovery of new knowledge about complex biological systems.

The Bioinformatics Resource Facility (BRF) provides general hardware and software support for all research groups of the CeBiTec within genome and post-genome projects. Altogether, the current BRF storing capacities add up to approx. 54 Terabyte disk storage and approx. 240 Terabyte tape storage. A high-performance compute cluster with more than 500 CPUs and an overall capacity of approx. 1,2 Teraflops is available for large scale computations like whole genome annotations.

In addition to extensive hardware resources, data management for genome and post-genome research requires new software solutions for systematic data acquisition, secure storage of structured information, and different levels of controlled data access for a large interdisciplinary spectrum of users, enabling scientists to browse through a hierarchy of data ranging from raw samples to highly structured complexes.

Within the last seven years, the BRF developed a comprehensive bioinformatics platform for genome and post-genome research. Services of the platform concerning genomics comprise the maintenance and annotation of complete bacterial genomes as well as the evaluation of other sequence data employing the GenDB (Fig. 1), (Meyer *et al*. 2003) and SAMS software. While the GenDB system was successfully used for the automatic and manual annotation of a dozen microbial genomes, SAMS is currently applied for detailed analysis of large sequence sets (e.g. ESTs or SBS sequencing reads). In the field of transcriptomics, the

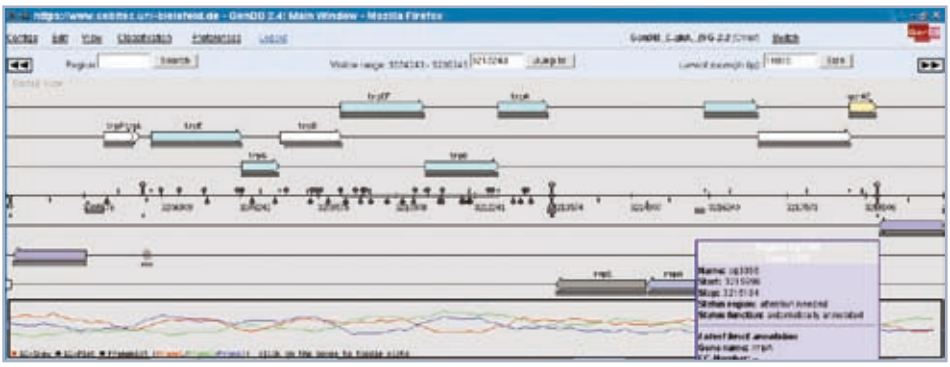

Fig 1: This screenshot shows the main window of the GenDB web interface. Depicted here is the tryptophan operon of *C. glutamicum* with serveral insertion sites of transposable elements and terminator regions. Genes are colored according to their COG category.

EMMA (Dondrup *et al*. 2003) software is provided as a MAGE compliant software platform for the evaluation of data resulting from genome-wide transcriptomic studies. Detailed experimental setups and protocols as well as all raw data sets are stored in a separate LIMS component (ArrayLIMS). ProDB (Wilke *et al*. 2003) is software for large-scale analysis of proteome data, also including a LIMS component. ProDB stores experimental data, such as images of 2D gels or mass spectra and allows automated data analysis and annotation of mass spectra. Data access across different components is mediated *via* the BRIDGE layer (Goesmann *et al*. 2003, Goesmann *et al*. 2005).
Currently, service of the BRF is employed in the following national and international research projects:

- GenoMik-Plus network 'Functional Genome Research on Bacteria relevant for Agriculture, Environment an Biotechnology' (BMBF)
- 'SysMap - System-oriented analysis of the central metabolism of microbial amino acid producers' (BMBF)
- 'QuantPro: Quantitative analysis of the membrane proteome of Gram-positive bacteria' (BMBF)
- GRAIN LEGUMES Integrated Project - GLIP (EU)
- MARINE GENOMICS (EU)

Future Projects and Aims

The concept of developing in-house software systems that are exactly tailored to the needs and requirements within a project has proven to be very successful. Nevertheless, ongoing research and development of novel tools and databases is essential for future approaches also towards systems biology. Thus, we are planning to further elaborate the Bielefeld software suite illustrated in Fig. 2 and provide researchers with advanced data analysis, data mining, and visualization facilities. Therefore, we continue the development of open source analysis tools in the area of genome, transcriptome, proteome, and metabolome research. The major goal is to develop novel approaches for data mining and visualization of heterogeneous data sets emerging in systems biology research.

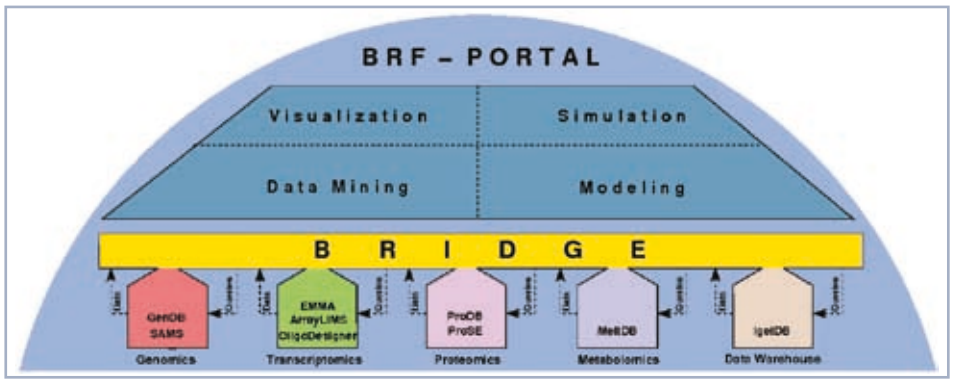

Fig 2: The BRF bioinformatics software platform for genome and post-genome data management, data analysis, and data integration. The platform comprises software for high-throughput sequence analysis (SAMS) and genome annotation (GenDB), transcriptome (OligoDesigner, ArrayLIMS, and EMMA) and proteome (ProDB and ProSE) data analysis. Currently, a new software module for metabolome data analysis (MeltDB) and a Data Warehouse (IgetDB) for efficient queries on large data sets are being developed. All components are linked *via* the BRIDGE integration layer providing an interface for further data mining, modeling, simulation, and visualization approaches.

Selected publications

Goesmann, A. *et al*.: 2005. **BRIGEP - The BRIDGE-based genome-transcriptome-proteome browser.** Nucleic Acids Res., 33: W710-W160

Dondrup, M. *et al*.: 2003. **EMMA: A platform for consistent storage and efficient analysis of microarray data.** J. Biotechnol., 106: 135-146

Goesmann, A. *et al*.: 2003. **Building a BRIDGE for the integration of heterogeneous data from functional genomics into a platform for systems biology.** J. Biotechnol., 106: 157-167

Meyer, F. *et al*.: 2003. **GenDB--an open source genome annotation system for prokaryote genomes.** Nucleic Acids Res., 31: 2187-2195

Wilke, A. *et al*.: 2003. **Bioinformatics support for high-throughput proteomics.** J. Biotechnol., 106: 147-156

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