The Swammerdam Institute for Life Sciences

Annual Report 2010

Faculty of Science

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Faculty of Science
Swammerdam Institute for Life Sciences
Annual report 2010

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Science Park 904, photos by Muus de Haan

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Preface by the director

The Swammerdam Institute for Life Sciences: developments in 2010

The most important development in 2010 was the relocation of the SILS research groups that were still housed at the Roeterseiland to the new building of the Faculty of Science at the Science Park Amsterdam. Finally, ten years after the establishment of SILS, all personnel is now housed together in state-of-the-art laboratory facilities and offices, which will definitively lead to more extensive sharing of knowledge, facilities and equipment between the different groups. All eight research institutes of the Faculty of Science, its teaching organisation and its directorate are now housed together in a building having a length of 260 meters, a width of 50 to 100 meters and a height of 26 meters.

In 2010 the number of bachelors that enrolled for the first time in one of the programmes of the Faculty of Science increased to over 1000. Fifty five percent of them have chosen Biomedical Sciences, Psychobiology or Biology, which are bachelor programmes to which SILS staff contributes substantially. The number of students that chose one of the master programmes that are organised by SILS or have a substantial SILS involvement, i.e. Biomedical Sciences, Brain & Cognition, Biology and Life Sciences/Systems Biology, increased substantially as well. Noteworthy is the success of the new master track Psychopharmacology and Pathophysiology that attracted 20 students at the start. Income of SILS out of educational activities in 2010 reached M€ 1,8.

Ten PhD students E. Lee, C. Oomen, S. Arisz, D. Vis, C. Rubingh, R. Orij, E. van Velzen, M. Nessen, L. Smit-Rigter and W. Huijbers who were employed by SILS and supervised by one of the full professors of SILS, defended their thesis in 2010 while two PhD students, V. Peperzak and C. Maas, were supervised by Prof. dr. J. Borst of the Netherlands Cancer Institute, who is a SILS professor by special appointment.

Next to 28 novel externally funded projects in 2010, personal grants were also awarded to four SILS scientists. Dr. M. Rep obtained a NWO VICI grant of k€ 1500 while dr. C. Fitzsimons, dr. M. Postma and dr. H. van den Burg each obtained a NWO VIDI grant of k€ 800. In total SILS staff obtained M€ 8.6 out of external research grants in 2010 on a total budget of M€ 19.

SILS' output regarding scientific publications reached an impressive 150 peer-reviewed publications. The highlights of 2010 were publications in Nature Methods (Th. Gadella, J. Goedhart, L. van Weeren, M. Hink and N. Vischer), Nature (M. Rep, C. van der Does, P. Houterman, and W. Jonkers), Science (R. Orij and G. Smits), Science (A. Otte) and Cell (T. den Blaauwen, B. van den Berg van Saparoea and J. Verheul).

Other activities in 2010 were the annual SILS Research Day organised by the SILS PhD/PD Council in June and, at the end of 2010, the SILS Retreat that was attended by 34 staff members. The research programmes of all groups were discussed, improvements of the organisation of SILS were suggested and developments in the life sciences in The Netherlands and the position of SILS in this exciting field evaluated. Overall it was concluded that in the coming years there are enough opportunities to further improve SILS' performance and promise a bright future.

Finally, in July dr. H.D. Veldhuis, left SILS after 5 years of being in charge of the institute.

Prof. dr. W.J. Stiekema
director

Research groups within the Swammerdam Institute for Life Sciences

Systems Biology of the Living Cell

Molecular Microbial Physiology	Prof.dr. K.J. Hellingwerf
Molecular Biology and Microbial Food Safety	Prof.dr. S. Brul
Nuclear Organisation	Prof.dr. R. van Driel
Epigenetic Regulation of Gene Expression	Prof.dr. A.P. Otte
Molecular Cytology	Prof.dr. Th.W.J. Gadella

Plant Signalling

Plant Physiology	Prof.dr. M.A. Haring
Molecular Plant Pathology	Prof.dr. B.J.C. Cornelissen

SILS Center for NeuroScience

Cognitive and Systems Neuroscience	Prof.dr. C.M.A. Pennartz
Cellular and Systems Neurobiology	Prof.dr. W.J. Wadman
Structural and functional plasticity of the nervous system	Prof.dr. P.J.Lucassen

Life Science Technologies

Mass Spectrometry of Biomacromolecules	Prof.dr. C.G. de Koster
BioSystems Data Analysis	Prof.dr. A.K. Smilde
Micro Array Department and Integrated Bioinformatics Unit	Dr. T.M. Breit

Research Programme *Systems Biology of the Living Cell*

Molecular Microbial Physiology

Chairholder: Prof. dr. K.J. Hellingwerf

Prof. dr. M.J. Teixeira de Mattos	Professor
Prof. dr. J. Hugenholtz	Special Chair

Introduction

The impact that microbes exert on life on Earth and indeed on Earth itself has been well-recognised now for many decades. The activity of microorganisms is not seen only at the global levels of evolution, the cycle of elements, ecological interactions and so on, but also affects human life directly both for better and for worse. Our knowledge about the biochemistry and physiology of microbial species is extensive but in many cases, however, only descriptive and qualitative. Further understanding of the impressive potential of microbes to adapt, proliferate and survive under a vast range of conditions demands a quantitative and systems-analytical approach. This is even more so when it comes either to combating the adverse properties of microbes or to apply their many beneficial capacities, that is, transforming fundamental insights into applications. The Molecular Microbial Physiology Group (MMPG) has recognised the need for the "new" quantitative microbiology and has in the past years shifted its research accordingly to what may be called Systems Microbiology. Our research deals with integrating the properties of biochemical/biophysical networks such as glycolysis, photosynthesis and respiration with signal transduction and signal processing, with structure-function relations and with physiological strategies for survival and growth. This integrative approach goes hand in hand with studies on specific (sub)molecular events (e.g. in proteins involved in light sensing or the regulatory role of electron carriers in the redox chemistry of the chemotrophic cell). The work aims at understanding how their life style endows microbes with the capacity to successfully cope with often severe and ever-changing environments.

The broad diversity of microbial genera, and the large genetic, biochemical and physiological differences between the genera, makes it unavoidable to focus the research on more than one species. We study both chemoheterotrophs, including the Gram-positive, endospore-forming *Bacillus subtilis*, industrially relevant Lactic Acid Bacteria and the metabolically extremely versatile Gram-negative *Escherichia coli,* and the model organism for oxygenic photosynthesis: *Synechocystis.* For a large part our interest in Lactic Acid Bacteria stems from the expertise of Professor Hugenholtz. This year he moved from the Dutch Institute for Dairy Research (NIZO) to the Coca Cola Company where he will be the Director of the Fermentation Research Center in Germany. Nevertheless his activities with respect to teaching and supervision of research within our group will be continued.

Research Highlights

- Our work on the significance of the respiratory chain of *E. coli*, being branched and partially uncoupled from energy conservation, has attracted much attention. New collaborations have been initiated to confirm the challenging suggestion that alternative catabolic routes are of much more importance than expected to

date. Furthermore, the role of the various quinone species as key redox signals has become apparent.

- The SUMO-2 project (a second NWO-grant as part of the transnational SysMo-2 initiative) has started this year: the physiological and biochemical characterisation of relevant mutants is now being carried out to provide data for a kinetic model of the respiratory chain that is being constructed in collaboration with Dr F. Bruggeman.
- Another follow-up Sysmo project, SysmoLAB has been awarded. Here, the aim is to model catabolism in lactic acid bacteria. The most challenging finding was made that the well-known catabolic switch from homolactic to mixed acid fermentation, invoked by the availability of external energy resources, is mainly controlled by the allosteric regulators Fructose-*bis*-phosphate and Glyceraldehyde-phosphate rather than by changes in gene expression.
- An important observation has been made related to the functional photocycle of Photoactive Yellow Protein. For the first time direct evidence has been provided that the photo-isomerization of the ethylene bond of the chromophore of PYP has to be accompanied by additional single-bond rotation. A multidisciplinary comparison (using a.o. picosecond time-resolved IR studies and molecular dynamics simulations) of the photochemistry of a set of mutant proteins has resulted in a consistent picture of the photo-isomerization event: as the carbonyl group of the chromophore is held more and more strongly, e.g. through the formation of multiple hydrogen bonds, the quantum yield of photo-isomerization of PYP decreases progressively. By the use of another set of mutant PYP proteins, which allow tryptophan fluorescence to monitor the entry of hydrated protons into the main hydrophobic core of the protein, we are resolving the sequential events of proton transfer to the chromophore, a key step that has to take place before the signalling state of PYP can be formed. This work is carried out in close collaboration with Profs. Groot and Van Grondelle (Vrije University Amsterdam), Larsen (UC Davis, Ca, USA) and Boelens (University of Utrecht).
- The general stress response (GSR) of the chemotrophic Gram-positive *Bacillus subtilis* can be activated by diverse input signals ranging from energy limitations to salt-, ethanol- or heat-shock. Our group has shown that blue light also acts as an activator. Induction is under control of a photoreceptor protein called YtvA, which exerts its function through a large protein complex called the stressosome. We have discovered a (chronologically) second effect of light on the activation of the GSR, regulated by the RsbP/Q pathway that also relays information on energy stress to the cells.
- Our research on the use of photosynthetic cyanobacteria for the production of a variety of products from CO_2 continues steadily. Site-directed insertions of gene-cassettes from fermentative organisms into the photosynthetic *Synechocystis* sp. PCC 6803 have been obtained resulting in organisms that are able to produce ethanol. The same approach was used successfully for lactate and ethene. Now we will extend this to other products like butanol. In addition, we focus on elucidating how environmental conditions and intracellular metabolic regulation affect the flux to these products, at the genetic, biochemical and physiological level.

Other Highlights

- The core patent that describes the technology to engineer photosynthetic cyanobacteria for the production of valuable chemicals has been registered.
- A research proposal entitled: “Expanding society’s toolbox to harvest solar energy: Creating multi-scale computational models to optimize oxygenic photosynthesis” (coordinator: Prof. Hellingwerf and submitted under the call “Towards BioSolar Cells” of FOM/ALW) has been granted to a consortium

of UvA, VUA, WUR, AMOLF and CWI. We anticipate that a group of five PhD students will take up this challenging task.

- A grant application by Photanol BV for the "Bioraffinage" theme financed by the Ministries of Economic Affairs and Agriculture, Nature and Food (LNV) was ranked as #1 in the Netherlands and awarded as of August 2010. The grant will be applied for the design, construction and running of a pilot plant. The plant will be housed in the greenhouse of the Faculty at Science Park.
- Prof. Hellingwerf, as a co-applicant with Prof. Van Grondelle (VUA) has been invited by FOM/NOW to submit a grant proposal to found a national Focus Group for research on "Fuel by Photosynthesis".

Research aims for the coming year

- The two Sysmo projects will continue to integrate the physiological and biochemical experimental data with the modelling. For SUMO, a kinetic model will be constructed that includes kinetic data on components of the respiratory chain from literature and obtained from our own experiments. Data will include non-steady state analysis of fluxes and metabolites. The model will include proton gradients and eventually the proton motive force. Finally, such a kinetic model will be linked to existing models and models under construction that describe other catabolic units, such as transport, glycolysis and tca cycle. Related to this subject will be the investigation on the role of alternative glycolytic pathways/enzymes to further unravel the energetic efficiency of catabolism. For SysmoLAB, we will aim at pinpointing the biochemical and genetic control points that define the differences between different lactic acid bacteria.
- Photofermentation research will not just continue along the current lines but be strengthened by the start of the TBSC initiative. Besides focus on photofermentative production of butanol and related intermediates, fundamental research that includes a systems biological analysis of the effects of inserting heterologous pathways in primary metabolic routes will be enhanced. As for the previous period, pathway expression will be optimized through gene-amplification strategies.
- Site-directed mutagenesis, combined with high resolution time-resolved spectrometric technologies will continue to be an important tool in our studies on microbial photoreceptor and photosignalling structures, functions and mechanisms.
- Mutant strains of *Lactobacillus johnsonii*, lacking one or more of the hydrogen peroxide producing systems will be made available by our collaborators at Nestlé, Zurich, Switzerland. This will be very helpful in the NIZO-UvA research collaboration on stress response, population heterogeneity and survival of this probiotic organism. Time-resolved transcriptome analyses will be carried out on perturbed (e.g. anaerobic/aerobic transitions) steady state cultures to describe the events that precede and accompany the stress response.

Molecular Biology and Microbial Food Safety

Chairholder: Prof. dr. S. Brul

Dr. J.C. van der Spek	Assistant Professor
Dr. G.J. Smits	Assistant Professor
Dr. F.M. Klis	Senior scientist (former Associate Professor)
Dr. B. Ter Kuile	Researcher Dutch Food & Drug Authority (VWA)

Introduction

2010 saw a strengthening of the group in relation to our efforts on fundamental understanding of **stress response** mechanisms in (**micro)organisms**. We focus on the bioenergetics of the response as well as on pHi homeostasis. Both are topical and relate to homeostasis in yeast and the simple multicellular eukaryote *Caenorhabditis elegans.* The latter is used where single cell eukaryotes are insufficient to explain a stress phenotype. In the McGillavry application round for excellent young talent we were successful in attracting a young PI from Stanford University who will reinforce the *C. elegans* team. A prime topic is the development of reactive oxygen species-derived damage as a consequence of energy stress. Some 10 years ago, as a spin-off of the yeast work, we started studies in the field of bacterial spore formers starting from the same questions on bioenergetics and pHi maintenance driven by demands from practice where weak-organic acids are used as prime food preservatives. Such application-driven research also include elevated temperature and antibiotic stress. Finally, in the framework of a large EU consortium we focus on putting our knowledge of *Candida* cell wall proteins to use for the development of vaccines. In 2010, we converted our work into 15 publications most of which were published before the end of the year. Most notably, Dr. Gertien Smits and our PhD student Rick Orij were co-authors of a paper in Science. The group expanded to over 20 staff members and provided internships to ~10 bachelor and master students indicating vitality and viability.

Future Prospects & Societal impact

Spin-off of our studies in society aims at contributing to improved food safety in close collaboration with the Dutch Food Safety Authority (Havelaar et al., 2010). To this end a new 4-year contract for sponsoring of research on antibiotic resistance was secured. Secondly, the group continues to deliver data with the STW-sponsored post-doctoral fellow Alex Ter Beek to the benefit of the discovery of the Achilles heel of food spoilage bacterial spore formers. Thirdly, we are key players in a large European project on vaccine development against an important group of infectious diseases caused by *Candida albicans*. In this context, group leader prof. Brul was asked to organise a symposium at the large 2011 FEMS European Congres of Microbiology in Geneve. We actively pursue patent opportunities in the application areas of our research.

Research Highlights

- A collaboration with the Canadian research group of Dr. Chris Loewen resulted in co-authorships on a Science publication describing the role of the intracellular pH in regulating the inositol biosynthesis and thus tuning lipid metabolism to the availability of sugar substrate (Young et al. 2010). The paper was part of the PhD thesis of our PhD student Rick Orij who successfully defended his thesis. The introduction of the thesis has meanwhile been converted into a review for BBA on the behaviour of the intracellular pH in eukaryotic cells focusing on yeast. Furthermore, in all studies a systems approach is advocated. We contributed with 4 authors together with the researchers of the Free University and the TU-Delft to a paper in FEBS journal (van Eunen, 2010) that set standards for the measurement of enzyme activities under in vivo-like conditions for systems biology. The paper won a prestigious prize of the European Federation

for Biochemical Societies as the best paper published in 2010 in the journal by a young first author scientist.

- In 2010 our group was successful in a collaborative effort with the de Mass Spectrometry of Biomacromolecules Group of de Koster and the Molecular Microbial Physiology Group of Hellingwerf in the quantification of the *Candida albicans* cell wall proteome in response to the environmental pH, crucial to health and disease (Sosinska et al., 2010). Work in our group in collaboration with the de Koster group at SILS has subsequently focused on establishing a comprehensive quantitative proteomics analysis of the hyphal and yeast form of *Candida* in response to a wide array of hyphal inducers (Heilmann et al. 2011, under final review). In addition, we have covered the secretome of the pathogenic yeast (Sorgo et al., 2010), providing markers for monitoring the presence of *Candida* cells in body fluids. A fully updated review of the presence and importance of yeast cell wall proteins was published (Klis et al., 2010). The proteomics analysis of microbial cell walls was extended to the bacterial spores by ERASMUS MUNDUS fellow Wishwas Abhyankar (Brul et al. appeared in 2011 Food Microbiology; Abhyankar et al. Proteomics under revision).
- In our line of research on bacterial spore-formers we continued our studies on bacterial spore germination and outgrowth inhibition in the framework of an STW-sponsored project. A prime focus is on enhancing the efficacy of weak organic acids for this purpose (Ter Beek and Brul, 2010). Furthermore, we established experimental systems to analyse the stress resistant coat of Bacillus spores (above) as well as to assess at single spore level germination and outgrowth, using live imaging techniques (Ter Beek et al., appeared in 2011 Food Microbiology; Pandey, 2011 submitted). Both sponsored by ERASMUS Mundus and the latter in close collaboration with the Centre for Advanced Microscopy of SILS (Prof. E. Manders).
- The bacterial research-line focusing on antibiotic resistance development directly linked to microbial food safety, continued to run in close collaboration with the Dutch Food Safety Authority (VWA). The data show that resistance acquisition of bacteria to fluoroquinolone exposure can be very rapid (Schuurmans et al. 2010). Such resistance can be both adaptation-driven as well as occur de novo and is not limited to this type of antibiotics (van der Horst et al. 2011). Genome sequencing studies were successfully initiated with the AMC group of Frank Baas. Challenges to microbial food preservation were extensively discussed (Havelaar et al., 2010).

Other Highlights

*S. Brul***:** FEMS representative of the Dutch Society for Microbiology as of 2009; Chair of the Dutch Institute for BioScience; editor Elsevier's Food Microbiology; STW fellowship started; FES funds (Nanonext) secured; VWA grant applied for (meanwhile assured); member of the STW VICI committee and EU FP7 project reviews.
F.M. Klis: Editor Eukaryotic Cell, FEMS Yeast Research, Yeast.
McGillavry fellow: Y. Budovskaya from Stanford reinforces our *Caenorhabditis elegans* model work.

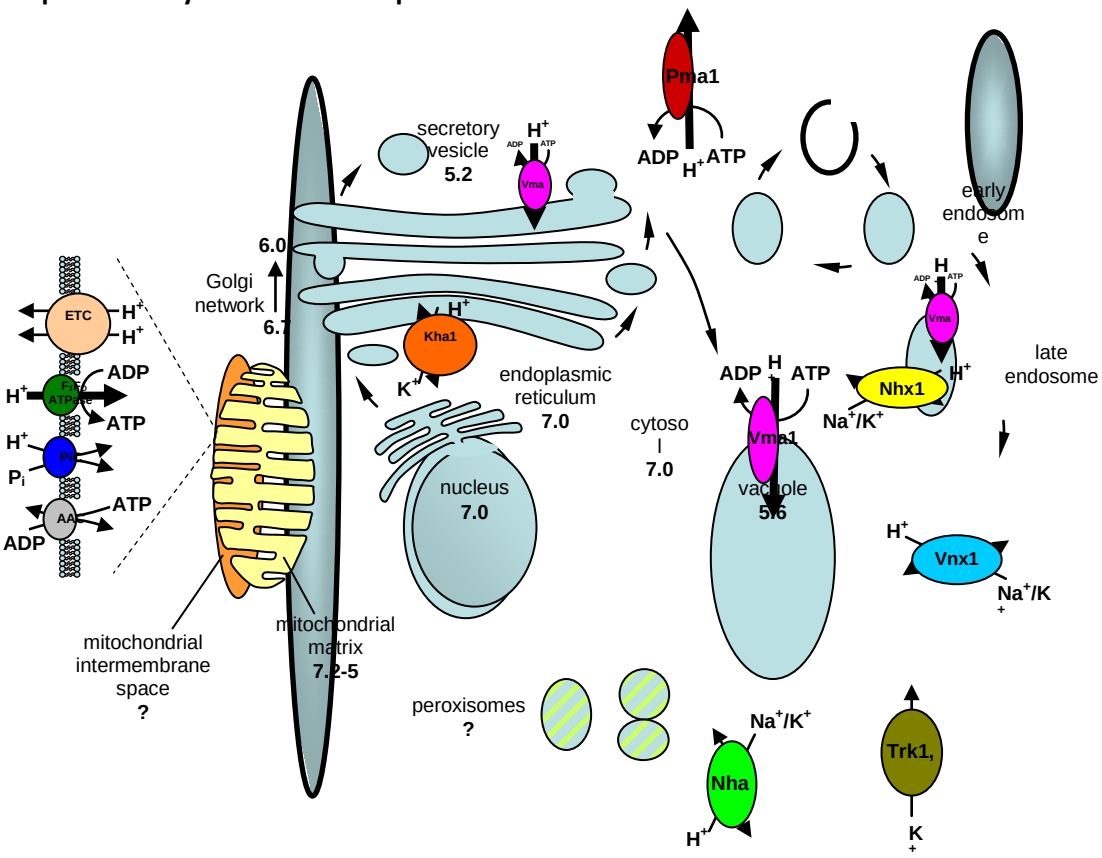
Research aims for the coming year

- *Weak organic acid stress mechanisms; what is the role of energy metabolism and which are the efficient long term responses.* In the study of yeast and *Bacillus* energy metabolism and short term stress response against these compounds we focus on both second scale time-resolved measurements of intracellular pH perturbation, verification of membrane potential as well as membrane structural long-term adaptations. With the department of Mass Spectrometry of Biomacromolecules we will set up a system in yeast and *C. elegans* to assess the energy stress induced ROS-dependent cellular damage (see also ageing stress).
- *The mechanisms of temperature stress response and resistance.* This research line includes vegetative stress response to thermal stress as well as bacterial spore response towards extreme thermal challenge. The line on vegetative stress will be concluded with the PhD defense by student Jarne Postmus

(fulfilled 2011). Further efforts in the field will focus on an analysis of bacterial spore thermal resistance. We will analyse heat damage repair systems and characterise the primary protein composition of the spore (coat). Single spore germination and outgrowth data will be gathered using live imaging.

- *Antibiotic / mycotic stress response.* Here we will continue our work on the detailed proteomic analysis of the *Candida* cell wall proteins for vaccine generation against this medically relevant yeast in collaboration with Dr. Mihai Netea (Nijmegen). In a preventative setting the studies on antibiotic resistance development will be continued and expanded to include genome wide sequence data.
- *Mechanisms of ageing (stress).* This new line of research by the McGillavry fellow will be affirmed. We will initiate a collaborative project to study the molecular mechanisms of ageing in *C. elegans* together with the Center for Advanced Microscopy (prof. E. Manders) and the department of Mass Spectrometry of Biomacromolecules (prof. C. de Koster). In particular we are planning to establish methodology to study effect of ageing, diet, and stress on protein oxidation throughout the life span of nematodes using quantitative proteomics.

pH in eukaryotic cellular compartments



Nuclear Organisation

Chairholder: Prof.dr. R. van Driel

Dr. P.F. Fransz	Assistant Professor
Dr. M.E. Stam	Assistant Professor
Dr. P.J. Verschure	Assistant Professor

Introduction

Nuclear Organisation Group (NOG)
Gene expression is controlled by different mechanisms, including epigenetic modifications, intra-and interchromosomal interactions and chromatin folding. Our mission is to understand how these mechanisms control genome activity together. We concentrate on the dynamics of chromatin structure in relation to gene expression and DNA repair. Our methodology involves a multi-disciplinary approach combining microscopic, molecular, biochemical and genetic analyses, and mathematical modelling. Predictive mathematical modelling is used to develop precise quantitative working hypotheses that constitute the basis of our experiments. The functional relationship between gene regulation, nuclear organisation and chromatin structure is evolutionary conserved in eukaryotic cells. Combining information from different model systems gives us unique insights into structure-function relationships of the eukaryotic genome inside the nucleus.

Research Highlights

Paul Fransz and colleagues published the intriguing phenomenon of light-induced reorganisation of chromatin, which is a reversible process and regulated by the photoreceptors CRY2 and PHYB. A model is proposed in which light controls chromatin decompaction via CRY2 and PHYB. The data support the concept that stress and developmental changes trigger responses in the global organisation of chromatin.
Maike Stam and colleagues published findings providing insight into the mechanisms underlying paramutation and tissue-specific regulation at the chromatin structure level in maize. Their results indicate a role for DNA methylation in the establishment and heritable maintenance of a silenced chromatin state, while histone modifications appear mainly involved in tissue-specific regulation of gene expression.
Roel van Driel and coworkers continued the systems biology projects on (i) *in vivo* assembly and functional behaviour of chromatin-associated multi-protein complexes, and (ii) folding of the chromatin fibre in the interphase nucleus in relation to local transcriptional activity. In both cases key predictions made by recently published quantitative models were tested experimentally. Results are translated to updated models, creating new insights into the functioning and underlying principles of these nuclear systems.
Pernette Verschure and colleagues created computational models explaining stochastic gene activity as well as 'spreading' of the epigenetic state over nucleosomes to predict the behaviour of epigenetically toggled synthetic mammalian cell systems. The experimental measurements of the epigenetically modulated state within these systems are ongoing.

Other Highlights

Roel van Driel is director of the national NGI-funded research programme Netherlands Consortium for Systems Biology (NCSB) and advisor of several German national systems biology programmes. Pernette Verschure chaired the executive board of the Women in the Faculty network (WiF). Maike Stam was independent member of the appointment advisory committee on the MacGillavry tenure track for woman at the FNWI.
Verschure, P.J. (2010). Epigenetic gene regulation of the eukaryotic genome: Sytems Biology approaches using synthetic cell systems. The EMBO meeting Barcelona 2010: Barcelona, Spain.
Verschure, P.J. (2010). Mammalian Synthetic Biology from tools to therapies. Organisation of

Mini-symposium (SILS-NISB): Amsterdam, the Netherlands (2010, December 09).

Research aims for the coming year

Fransz and colleagues

Our aim is to assess the relationship between chromosome folding and nuclear reprogramming and to investigate long-range chromosome interactions. The research in 2011 will concentrate on (1) tracking an entire chromosome during interphase and (2) setting up experiments to study chromosome looping in collaboration with M. Stam.

Stam and colleagues

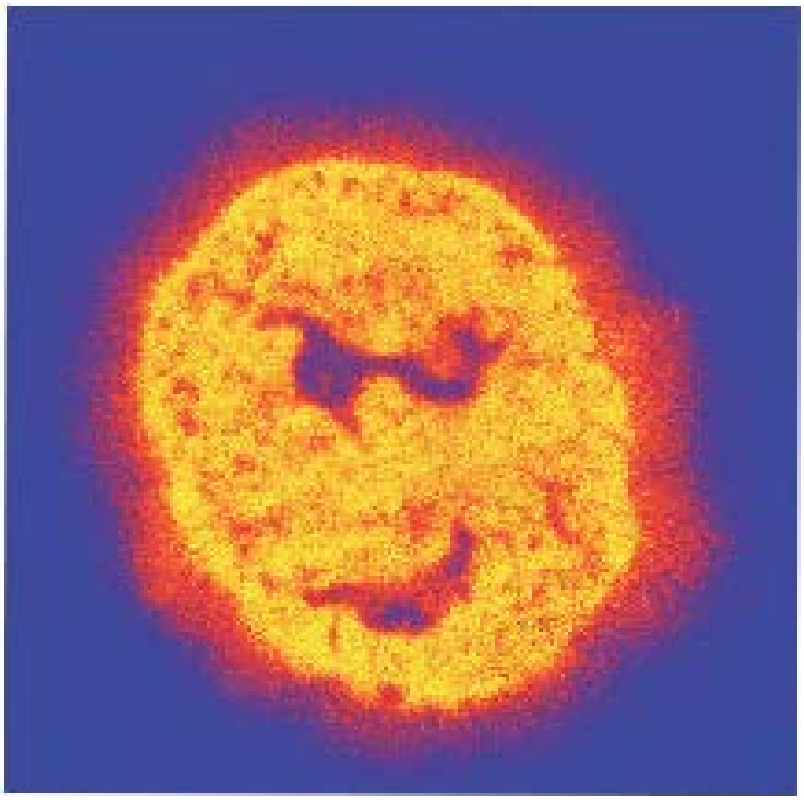
The general aim is to get insight into the functional relation between gene activity, epigenetic mechanisms and chromosomal interactions. Together with P. Fransz, in 2011 a study in Arabidopsis will be started in which the generated data will be used in mathematical modelling to establish quantitative relationships between chromatin folding and gene activity (collaboration with Prof. Heermann, Heidelberg, Germany).

Van Driel and coworkers

The two systems biology projects will be continued, focusing on experimental results that do not agree with the present versions of the predictive models. Updating the models in collaboration with the Heermann and the Höfer groups, both in Heidelberg, will have priority. In particular, we will put effort in unveiling novel emerging system properties.

Verschure and colleagues

We expand our research to understand design principles of epigenetic regulation: (1) real-time transcription measurements, (2) single-cell/molecule transcript counting combined with mathematical modelling to study a set of variably regulated mammalian genes (3) (epi)genetic network behaviour of Huntington's disease onset using bioinformatics and computational models (HD) (collaboration Dr. A. Kremer ErasmusMC).



Fluorescent DNA halo.
Upon permeabilization and treatment of nuclei with high-salt buffers, supercoiled DNA loops unwind and form a halo (red) around an insoluble nuclear scaffold (yellow). The technique is used for estimating the average length of DNA loops in interphase nuclei.

Epigenetic Regulation of Gene Expression

Chairholder: Prof. dr. A.P. Otte

Dr. Ir. J.A. Verhees Assistant Professor

Introduction

It is our aim to understand aspects of epigenetic regulation of gene expression. Research is focused on genomic elements that have a powerful, positive influence on promoter activity. These elements are employed to facilitate the production of therapeutic proteins in mammalian cell lines. However, the increased protein expression levels have a negative influence on cell growth. Very high protein expression levels force cells to stop growing, which is an undesirable phenomenon from a practical point of view. We attempt to understand this inverse relationship between protein expression levels and cell growth at a quantitative level. Furthermore, we develop inducible gene expression systems in which we can reversibly modulate protein expression levels and cell growth.

Research Highlights

We have identified novel genomic elements that are initiation points for high levels of transcription. These elements probably provide a more 'open' chromatin state in which a transfected gene that is flanked by these elements becomes more open for transcription. In order to develop novel inducible expression systems in which we can reversibly modulate protein expression levels and cell growth, we devised a novel set of selection markers. These markers include the Zeocin resistance protein, as well as markers that restore the synthesis of essential metabolic components that cells normally lack. Application of these markers warrants both high proteins expression levels as well as a high degree of stability of protein expression over prolonged periods of time.

Other Highlight

Director of a biotechnology company, CellaGenics, a spin-off company, emerging from SILS, FNWI and the UvA Holding in 2008. CellaGenics works in the research area of expression of therapeutic proteins and cell growth.

Future Prospects

In the coming year we will focus on further developing expression systems in which protein expression, growth rates of the cells and secretion of the proteins can be coordinately modulated to achieve an optimal expression platform for therapeutic proteins. As such we aim to investigate and modulate in a comprehensive way

1) the role of novel genomic elements in expression and stability of protein expression;
2) an inverse relationship between cell growth and protein expression levels.

We are also in the process of pursuing collaborations with industrial parties to evaluate our findings and to test our newly developed protein expression platform at an industrial scale.

Molecular Cytology

Chairholder: Prof.dr. T.W.J. Gadella

Dr. T. den Blaauwen	Assistant Professor
Dr. Ir. J. Goedhart	Assistant Professor
Dr. E. M. M. Manders	Assistant Professor
Dr. Ir. M.A. Hink	Assistant Professor

Introduction

Molecular Cytology & Centre for Advanced Microscopy (CAM):
Molecular Cytology is the study of the dynamic architecture of living cells. Our central theme is 'Self-organisation and signalling in living cells'. Self-organisation is the intrinsic property of matter to organise itself into a (dynamic) structure, whereas signalling implies the activity of gene-products to control a local activity, which can alter the local cellular architecture (e.g. driving morphogenesis). In order to achieve a certain 3D architecture in cells, these two important mechanisms work in concert. At Molecular Cytology both mechanisms are studied with emphasis on membrane-related architecture of living cells using advanced microscopy tools. The activities are connected to the Faculty of Science Spearhead programme on Systems Biology, where our contribution is on spatiotemporal systems biology of higher eukaryotes. The main research areas are:
1) *Spatial organisation of sub-cellular signalling* (group leaders prof. dr. T.W.J. Gadella, dr. J. Goedhart & dr. M.A. Hink). By employing genetic encoded fluorescent biosensors we analyse the in situ molecular interactions between signalling molecules (phospholipid-second messengers, receptors, G-proteins and effector molecules) and flow of information across and in the plane of the membrane of living mammalian cells. We aim to understand how cells can achieve and maintain a local signal in the membrane (e.g. in order to drive morphogenesis, or to define new cytoskeletal anchorage or vesicle-docking sites). The main pathways under study involve histamine/P2Y GPCR receptors, G-alfaQ to PLC activation triggering downstream calcium, kinase signalling and small GTPase (Rho/Rac/Cdc24) signalling. The close intertwining of several signalling cascades and our quantitative microscopy approach both necessitates and permits the generation of quantitative predictive modelling, which will effectively integrate this research line with Systems Biology approaches.
2) *Molecular dynamics of the bacterial cycle* (group leader dr. T. den Blaauwen). The morphology of rod shaped bacteria is achieved through two very dynamic synthetic complexes: the elongasome and the divisome. The elongasomes use the actin-like cytoskeleton MreB helix underneath the plasma membrane as a tracking device to elongate the cell envelope whereas the divisome is responsible for the division and synthesis of new cell poles. Cell division is directed by the FtsZ ring (a tubulin homolog), which exerts a small force on the bacterial envelope. The assembly and the dynamics of the elongasome and divisome are studied in vivo using immunofluorescence and fluorescence microscopy techniques (FRET, FRAP, localisation) and in vitro using state of the art biochemical and biophysical techniques. By aiming to obtain quantitative data, we hope to model the measured and observed interactions.
3) These research themes heavily depend on advanced microscopy technology organised within the *Centre for Advanced Microscopy* (CAM, 2004). The goal of CAM (em. prof. dr. G.J. Brakenhoff, prof. dr. T.W.J. Gadella, dr. E.M.M. Manders and dr. M. Hink) is to boost Life Sciences research using & developing (optical) microscopy techniques. Current most prominent developments are Controlled Light Exposure Microscopy (CLEM) (dr. Manders), multimode Fluorescence Lifetime Imaging Microscopy (FLIM)

(dr. Gadella), Spinning disk, Total Internal Reflection and PALM-microscopy (dr. Hink, Manders and Gadella) and Fluorescence (cross) correlation microscopy (dr. Hink).

Research Highlights

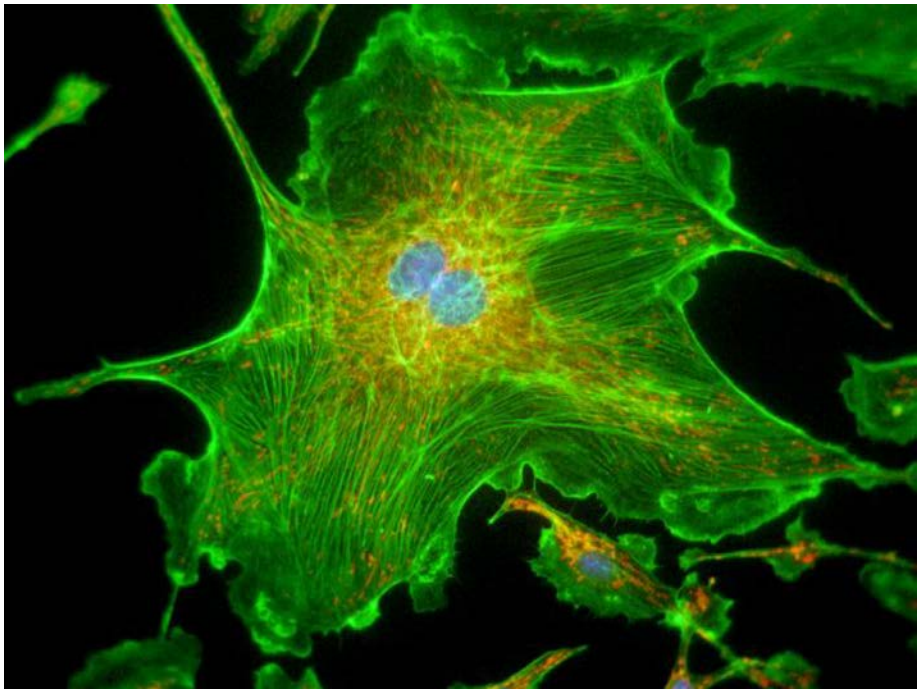
- Main scientific achievements in 2010 were the publication in Nature Methods of mTurquoise, the brightest cyan fluorescent protein to date, and the elucidation of a regulation mechanism for peptidoglycan synthesis in the cell wall of *E. coli*, published in Cell.
- In 2010 the van Leeuwenhoek Centre for Advanced Microscopy (LCAM) was founded as a formal collaboration between the Centre for Advanced Microscopy (SILS), the Centre for Microscopy Research (CMO) at the AMC (prof. C. J. van Noorden) and the Cell Biophysics group at the NKI (dr. K. Jalink).
- In 2010 we successfully implemented super resolution microscopy (photoactivated localisation microscopy, PALM). Hereby we achieved an accuracy of 7 nm resolution in light microscopic objects. This is 30x below the diffraction-limited resolution.
- In 2010 a new high-end microscope was installed (funded by NWO middelgroot) allowing single-molecule analysis by advanced spectroscopic techniques.

Other Highlights

- Erik Manders was appointed as guest professor Microscopic Techniques at the faculty of Bioscience Engineering of the University of Ghent (Belgium).
- Marten Postma was awarded an NWO VIDI grant on “Computational modelling of *Cnidarian* embryogenesis” and joined the section of Molecular Cytology in April 2010. His activities are an integral part of the spatiotemporal systems biology research efforts of the section of Molecular Cytology.

Research aims for the coming year

- To start a new master trajectory Cell Biology and Advanced Microscopy in the Biomedical Sciences Master programme with the LCAM partners.
- To publish on enhanced sensors for signal transduction based on mTurquoise
- To publish a new labelling method to study the growth of peptidoglycan in living cells and publish on the temporal interaction of the elongasome and divisome.
- To publish on the characterisation and application of new large Stokes-shift fluorescent proteins



Hela cell with fluorescently stained actin, mitochondria and nuclei.

Research Programme Plant Signalling

Plant Physiology

Chairholder: Prof. dr. M.A. Haring

Dr. Ir. R. C. Schuurink	Associate Professor
Dr. T. Munnik	Associate Professor
Dr. C. Testerink	Assistant Professor

Introduction

The Plant Physiology group investigates plant signalling at the cellular level and at the level of the whole plant. Our phospholipid signalling research is focused on the biological function of phosphatidic acid (PA) and polyphosphoinositides (PPIs). To visualise lipid signalling at the cellular level, we have developed genetically encoded-lipid biosensors for PA, PI3P, PI4P, DAG, PS and PI(4,5)P_2. Knockout lines of individual *PIK* (11), *PIPK* (11), *PLC* (9), *DGK* (7) and *PLD* (12) genes in *Arabidopsis* plants, are used to elucidate their role in stress signalling and development. An important research goal is to elucidate how PA modulates protein function and downstream plant responses. To this end we are studying the effect of PA on several protein kinases, including CTR1, SnRKs, PDK1 and PID. To study the biochemistry of scent of Petunia flowers we investigate transcription factors involved in regulating volatile benzenoid and phenylpropanoid synthesis and emission. Because plant volatiles that are important for interactions with insects are produced in leaf-hairs (trichomes) we are dissecting the metabolism of volatile terpenes in trichomes. RNA-Seq of trichome-ESTs from wild and cultivated tomato plants has provided us with a wealth of candidate genes. We are engineering the production of terpenoids in tomato trichomes in such a way that they become repellent for pest insects. Finally, we use Arabidopsis for transcriptomics and forward genetic screens to identify genes important in the response to the wound-induced C6-volatile *E*-2-hexenal and the subsequent signal GABA.

Research Highlights

Phospholipid research:

Recently, we discovered that heat stress (40°C) triggers two lipid signalling pathways, one through phospholipase D (PLD), generating phosphatidic acid (PA), and another via phosphatidylinositol 4-phosphate 5-kinase (PIPK), generating PIP_2. Both lipids are important second messengers in eukaryotes, functioning as membrane localised-docking sites for various protein targets. Using a genetically encoded-PIP_2 biosensor, i.e. a fusion of a PIP_2-specific lipid-binding domain with a fluorescent protein (FP; e.g. YFP) expressed in tobacco BY-2 cells, we found that heat stress triggers the formation of PIP_2 at the plasma membrane within minutes. Slightly later, unknown punctate structures appear in the cytosol that, after about 30 minutes, end up at the nuclear membrane. For PA, no such probe is yet available, so we have started to develop one. DNA constructs encoding 9 different PA-binding regions have been fused to an *FP*, while an additional 8 constructs have been made for controls, containing point mutations crucial for binding PA. Using T-DNA insertion KO-lines of *Arabidopsis thaliana*, we identified two *PLDs* that are involved in heat stress signalling. Moreover, double-mutants completely lost their heat stress-triggered PA response while the PIP_2 response was still intact. Microarray experiments and physiological assays will be used to establish PLD's function in the heat stress response, while an RNAi strategy will applied for the 3 remaining *PIPKs* for which no homozygous insertion lines could be found, to see whether they are

responsible for the heat stress-induced PIP_2 response.
We study intracellular signalling pathways linking salinity to root development and direction of root growth. These involve perception of high cytosolic Na^+ concentrations in the root, activation of lipid signalling and protein kinase activation, and modulation of endocytic pathways. We also investigate natural variation between Arabidopsis accessions, with the aim to identify novel loci contributing to optimal root growth in the presence of salinity or osmotic stress. One of the key players in stress signalling is the lipid second messenger phosphatidic acid (PA). Osmotic stress and salinity have been shown to induce the rapid and transient accumulation of PA. We have identified several protein kinases, including CTR1, SnRKs, PDK1 and PID, which selectively bind PA in vitro. Currently, we are investigating the relevance of PA-binding for function of these kinases in vivo, using mutant versions that can no longer bind PA. To increase our understanding of how lipid signals can affect downstream responses, we also study the molecular basis and structure of lipid-protein interactions (collaboration with Dr. E.E. Kooijman, Kent State, Ohio). In 2010, we have published our work on how anionic phospholipids, including PA, modulate activity of the phosphoenolpyruvate carboxylase enzyme of C_4 plants.

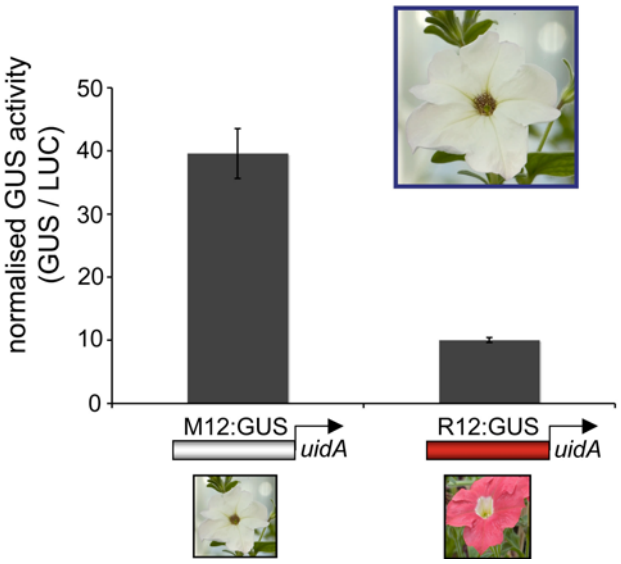
Plant volatiles research:
We focus on the role of C6 volatiles as signalling and priming molecules and have identified through forward genetic screens several E-2-hexenal response (her) Arabidopsis mutants. The her2 mutant has now been mapped, cloned and shown to encode an oxido-reductase in the mitochondria, of which we are trying to identify its specific activity. We are continuing our efforts to identify volatile terpenoids important in tomato-herbivore interactions. Through NMR and X-ray analysis we discovered that S. habrochaites makes actually 7-epizingiberene instead of alpha-zingiberene that is present in zinger. This 7-epizingiberene acts as a repellent to whiteflies while alpha-zingiberene does not. In order to identify transcription factors in the glandular trichomes of tomato that are involved in the regulation of terpene biosynthesis, two approaches are used: (1) Yeast one-hybrid and (2) Trichome RNA-Seq (GS FLX Titanium, 454 Life Sciences, USA). The Y1H screen yielded a putative TF binding to the Monoterpene synthase 1 (MTS1) promoter. This TF can transactivate MTS1p:GUS in leaves of *N.benthamiana* and we are currently constructing transgenic plants to study effects on the volatile terpenoid metabolome. Finally we try to identify the enzymes involved in synthesising sesquiterpenoid carboxylic acids toxic for spider mites.
In Petunia we have been able to identify motifs in the promoter of the R2R3-MYB ODORANT1 (ODO1) gene that determine volatile production in non-fragrant and fragrant petunias. We have identified the Petunia EOBII transcription factors as one of the regulators of ODO1. A specific target gene of ODO1 encodes an ABC transporter. RNAi lines for this gene show minor changes in volatile emission.

Other Highlights

Robert Schuurink: Keygene collaborative project (post-doc), 3 yrs: *Sucking Insect Resistance* (500k€).
Christa Testerink: NWO-ALW (post-doc) 3 yrs: *Novel salt stress-induced signals that control the direction of root growth* (250 k€).
Christa Testerink: NGI Horizon Breakthrough grant, 1,5 yrs: *Synthesis of phosphatidic acid (PA) on demand for a proteome-wide membrane recruitment screen* (100 k€).

Future Prospects

- Identification of the PA-binding site of the SnRK2, PID and PDK1 protein kinases
- To investigate the role of lipid signalling and protein kinases in the response of Arabidopsis roots to salt
- To analyse the results of a proteome-wide membrane recruitment screen of salt-induced PA-binding proteins
- To explore natural variation in Arabidopsis accessions for salt tolerance
- Develop and validate PA-FP biosensors
- Investigate the effects of altered terpene emission of transgenic tomato lines on insect behaviour
- Elucidate the functional role of the petunia ABC transporter regulated by ODO1



Agrobacterium tumefaciens-mediated transient assays in petunia petals of the fragrant petunia Mitchell (white) show that the 1.2kbp promoter of Mitchel (M12:GUS) is 4-times more active than the 1.2kbp promoter of the non-fragrant (red) petunia R27 (R12:GUS).

Molecular Plant Pathology

Chairholder: Prof. dr. B.J.C. Cornelissen

Dr. Ing. F. L. W. Takken Assistant Professor
Dr. M. Rep Assistant Professor

Introduction

Adapted pathogens cause disease by evading host defences that are aimed to restrict microbial proliferation. To reveal the molecular basis of resistance and susceptibility in plants we focus on the interaction between the fungus *Fusarium oxysporum* and susceptible and resistant tomato (*Solanum esculentum*) plants that carry the *I-2* resistance (*R*) gene. Besides I-2 we also study other (R) proteins that belong to the same family. Our specific interests are basal and induced defence mechanisms of the host, and virulence and avirulence factors of the pathogen.
The ability of a pathogen to colonise its host depends on 'general' pathogenicity genes as well as on specific, secreted 'effector' proteins. Effectors are called 'avirulence factors' when they are recognised by a matching R protein, thereby triggering disease resistance. For example, the R protein I-2 provides resistance of tomato to strains of *F. oxysporum* producing the effector Avr2 (Avirulence factor 2).
Our research aims at: (1) the identification and dissection of the protein complex(es) involved in R protein-mediated resistance. This work includes the functional analysis of individual complex-components and conformational changes in R proteins; (2) uncovering the role of pathogenicity genes and effector proteins (including avirulence factors) of *F. oxysporum* and identification of their targets in tomato; (3) unravelling the dynamics of genome evolution and the mechanisms of horizontal chromosome transfer in *F. oxysporum.*

Research Highlights

- This year a new project was started supported by a NWO-VICI grant to investigate the mechanism of chromosome transfer between fungi and the consequences of this remarkable phenomenon for the evolution of host-specific pathogenicity in the *F. oxysporum* species complex. A post-doc and two PhD students started on this project in September-November. The post-doc has established the melon-*F. oxysporum* system, with the aim of identifying effectors of *F.o. melonis* through melon xylem proteomics.
- First yeast two-hybrid (Y2H)-interactors of Avr1 and Avr2 have been identified in an effort to identify plant targets of this effector.
- After transient expression of *SIX6* in *N. benthamiana* leaves or after incubation of soybean roots with GFP-tagged Six6 protein, the protein was found to accumulate in plant nuclei.
- Surprisingly, deletion of *SIX5*, like deletion of *AVR2*, breaks *I-2*-mediated resistance. In the yeast two-hybrid system, Six5 interacts with Avr2, whereas Avr2 interacts with Avr1. The significance of these observations is unclear at present and under investigation.
- Transgenic tomato lines stably expressing *AVR2* show a distinct phenotype, possibly reflecting a change in hormone homeostasis.
- Transgenic Arabidopsis lines stably expressing *AVR2*, *SIX6* and *SIX8* show distinct phenotypes indicative for the presence of an effector-target in this non-host plant.
- Fol lines expressing fluorescently tagged Avr2 have been created to monitor the fate of Avr2 during infection. Preliminary data indicates that *AVR2* is strongly induced upon root contact and is also expressed during colonisation of xylem vessels. RFP-labelled Avr2 was found to localise inside host cells confirming its uptake from the xylem sap.
- Full-length MLA23, a barley powdery mildew resistance protein, was found to specifically co-purify with ADP, but not ATP, supporting our molecular "switch" model for NB-LRR proteins.
- Most R proteins are multi-domain proteins. Structure-function analyses of the tomato Mi-1 nematode resistance protein revealed that its extended N-terminal domain exerts both

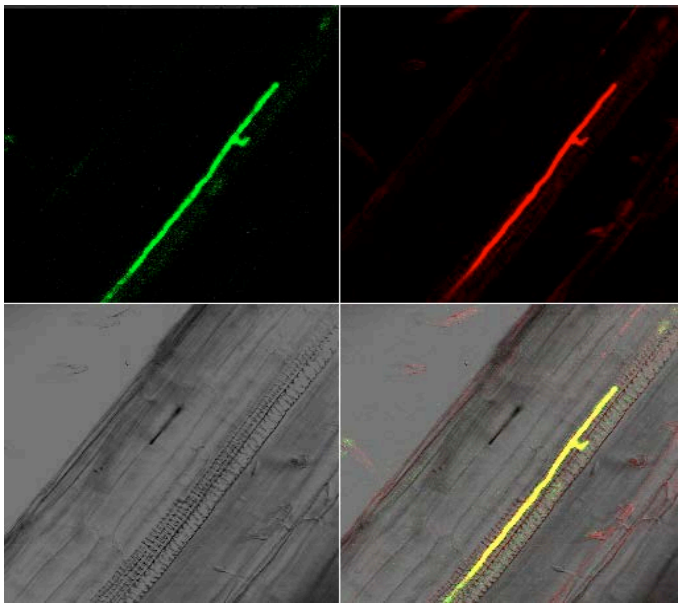
negative and positive regulatory functions. The minimal Mi-1 fragment able to trigger HR is the NT-2NB-LRR domain.
- Analysis of Arabidopsis plants in which SUMO (small ubiquitin-like modifier) isoforms were either silenced, knocked-out or over-expressed revealed that the different SUMO isoforms have non-redundant and specific functions in plant development and SA-mediated plant defences.

Other Highlights

Ben Cornelissen: (1) Panellist for the US National science foundation to serve in the advisory panel *Symbiosis, Defense and Self-recognition*, (2) Panelist for the Dutch NWO - ALW programme.

Research aims for the coming year

- To test the interaction of Avr1 with Y2H-identified interactors with other approaches: cytotrap, pull-down with *E.coli*-produced effector proteins.
- To initiate plant transformation to produce transgenic tomato plants expressing AVR1 or AVR3.
- To make a first set of targeted gene deletions in *F. oxysporum* to determine which processes are required for chromosome transfer.
- To identify transferrable chromosomes in *F. oxysporum f.sp. lycopersici* through a newly developed genetic screen.
- To make transgenic *F. oxysporum* strains expressing fluorescent proteins (split GFP system) to allow a first detailed analysis of cellular and nuclear processes occurring during hyphal fusion.
- To assemble novel *F. oxysporum* genome sequences in collaboration with Li-Jun Ma (Broad, Amherst) and explore new strategies for assignment of contigs to chromosomes.
- to identify effectors of *F. oxysporum f.sp. melonis* (Fom)
- To iIdentify additional effector genes on transferrable pathogenicity chromosome (chr14) of *F. oxysporum f.sp. lycopersici* through manual genome annotation, transcript detection and gene knock-out
- To delete and over-express the regulator gene SGE1 in different *formae speciales* of *F. oxysporum* and determine the effect on the transcriptome (RNAseq), secretome and cell wall proteome.
- Physical and functional analysis of the Six5-Avr2 interaction.
- To determine where in the host cell Avr2 exerts its virulence and avirulence functions by fusing Avr2 to various subcellular targeting sequences and analysing the obtained transgenic Fol strains in bioassays.
- To explore lipid-binding properties of Fol effector proteins.
- To analyse the ability and functional relevance of homo- and hetero-dimerisation of Fol effector proteins.
- Identification of host effector targets using proteomics.
- To finalise structure-function analysis of the Mi-1 N-terminus.



Confocal images of *Fusarium* colonising a xylem vessel of a susceptible tomato root.

In locus *Avr2* replacement in a *Fusarium* strain containing PS*ix1*:*GFP* with *PAvr2:RFP* reveals that Avr2 and Avr3 (Six1) are co-expressed during infection.

Research programme SILS - Center for Neuroscience

Cognitive and Systems Neuroscience

Chairholder: Prof. dr. C.M.A. Pennartz

Dr. W.E.J.M. Ghijsen	Assistant Professor
Dr. F.P. Battaglia	Assistant Professor
Dr. T. Kalenscher	Assistant Professor

Introduction

The group's global research aim is to elucidate how neuronal networks distributed across the prefrontal cortex, sensory neocortex, hippocampus and ventral striatum, cooperate in cognitive processes, including learning and memory consolidation, perception and multisensory integration. This aim is pursued using a variety of techniques and at various aggregate levels, ranging from cellular to systems and behavioural levels. The research focuses on the level of systems physiology. General research topics include:

- **The consolidation of memorised information** of recent experiences. A promising candidate mechanism for mediating this process is spontaneous "off-line" reactivation of stored information. After an initial experience which is marked by highly specific firing patterns in brain structures involved in memory, a replay of these firing patterns can be observed, with preservation of temporally specific features, such as the order in which brain cells fire. We pursue the causal relevance of this phenomenon for memory consolidation by electrical interventions, and how replay is orchestrated amongst different brain areas, such as the hippocampus and ventral striatum. Technically, this project is carried out in animals by performing ensemble recordings using ´tetrode arrays´ and by state-dependent deep brain stimulation techniques.
- We are also studying memory consolidation from **theoretical and computational viewpoints**. We are developing new computational models of memory consolidation and the formation of semantic memories, by making use of concepts from computational linguistics and Bayesian inference. Furthermore we develop new analytic methods to study coherence within and between cell assemblies in the brain, and how this coherence supports memory formation.
- Another main question in the field of learning and memory is how networks of cells collectively learn to generate **predictions about upcoming rewards**, based on sensory cues that precede reward delivery. Learning-related changes in rhythmic neural activity and network coherence are highlighted. We investigate which neurotransmitters and receptors influence the formation of neural representations of reward predictions. This line of research has been recently augmented by studying how stress hormones influence memory formation.
- We investigate relationships between **genes, learning and memory** capacities as measured in behaviour, and the systems physiology which forms the interface between gene expression and overt behaviour. These relationships are studied in the context of spatial navigation, conditioned place preference and cognitive flexibility in targeted knockout mice, e.g. regionally restricted NMDA receptor deletions in hippocampus and deletions of the *Arc* gene, which is involved in synaptic plasticity and AMPA receptor trafficking. This research line has been supplemented with a genetic mouse model of mental retardation (fragile-X syndrome).
- We investigate how neural assemblies in the brain cooperate to generate **conscious or**

unconscious multisensory representations, and how sensory inputs from different modalities are combined to achieve such integrated representations. A theoretical framework to understand consciousness as a process of multimodal integration is under construction, and we are moving to test its experimental predictions using *in vivo* 2-photon Calcium imaging and multi-area ensemble recordings. For instance, visual processing and tactile-visual integration are compared under awake and anaesthetised conditions. Moreover, the impact of the dimension of motivation and reward prediction on visual representations is studied using 2-photon-imaging of neural ensemble activity

Research Highlights

- Joint ensemble recordings were made from Hippocampus and Ventral striatum simultaneously to study how animals learn to predict reward value based on discrete cues and locations in the environment. In a Y-maze task, we found that sensory cues that predict reward elicit a switch in hippocampal representation. This is visible as an increase or decrease of firing rate of individual neurons for a variable time period, often locked to the duration of the sensory cues. Morover, ventral striatal ensembles appear to switch concurrently with the hippocampus. This indicates that a cue-elicited change in attentive-motivational state of the animal causes coordinated, robust changes in neural representations distributed over multiple brain areas.
- New measures of phase synchronisation between spikes and EEG (in relation to oscillatory field potentials) were developed. We showed that these measures are more robust in the face of volume-conduction, noise and sample-size bias than previously published methods.
- A key question regarding the neural basis of reinforcement learning concerns the role of the orbitofrontal cortex in coding reward expectancy and in using this information to direct behaviour. NMDA receptors are thought to be key elements in the neural mechanisms for remembering and learning to predict future rewards. We examine the role of these receptors in neural coding processes in the orbitofrontal cortex by combining tetrode recordings with local infusion of NMDA-R antagonist using reverse microdialysis. NMDA receptors were found to play an enhancing role in discrimination between and representation of different odours coupled to positive or negative trial outcomes, and in keeping firing rates under control to prevent premature responses and disinhibition.
- We studied the interactions between the hippocampus and the prefrontal cortex in rats during performance of a decision making task, and during the subsequent sleep. During behaviour, hippocampal/cortical coherence manifested itself in the form of oscillatory coherence and neural ensemble synchronisation. During sleep, transient replay events were observed in the prefrontal cortex, simultaneously with hippocampal sharp wave/ripples.
- We carried out an extensive set of experiments involving tetrode ensemble recordings in the hippocampus of control and NMDA receptor knockout mice, in a series of tasks, involving food search in a star-shape maze and running in a circular task, with the purpose of analysing the activity of hippocampal place cells when the NMDA receptor is functionally impaired. This study sheds new light on the role of synaptic plasticity in the plasticity of spatial representations and mechanisms underlying spike timing relative to theta rhythm. Similar ensemble recordings in mouse models related to mental retardation and Arc-dependent memory deficits have been conducted, and the results are currently under analysis.
- A 2-photon imaging setup was used to visualise the spatially and temporally ordered structure of neuronal population activity in the living mouse brain. To examine the characteristics of neural processing in conscious conditions, we compared how this structure differs between the awake and anaesthetised state. In the anaesthetised state, correlations between neural resting activity were on average higher and spatially spread out further than in the awake state. Functional clustering of neurons, manifested by spontaneous activity correlations, appears sparser and more sharply

delineated during consciousness than under anaesthesia.
- To investigate how neural assemblies in brain areas belonging to different sensory modality interact, we developed a new behavioural task in which visual and tactile inputs can be separately manipulated. Next we applied ensemble recording techniques to record four neocortical and hippocampal areas simultaneously (i.e. visual cortex, somatosensory cortex, perirhinal cortex and hippocampus). The results from this unique recording approach are currently being analysed.
- The hippocampus is thought to play a crucial role in representation of an animal´s location and, more in general, in representation of its internal and external state. However, it is unknown if it may also function in representing state parameters of other agents in the environment, e.g. conspecifics. A new behavioural protocol was developed to study whether rats can discriminate positions and movements of robotic agents in the environment. This was indeed the case. Preliminary results indicate that the hippocampus harbours cells sensitive to the position of external agents.

Other Highlights

- The group published 5 papers in high-impact journals, *viz.* J. Neuroscience (2X Van Wingerden et al.), Neuroimage (Vinck et al.; Daselaar et al.) and Neuron (Benchenane et al.).
- Cyriel Pennartz was appointed Chairman of the committee on Medium-size Equipment Investments in the Medical Sciences (Zon-Mw).
- Cyriel Pennartz was appointed Board member of the NWO committee on multidisciplinary Top grant reviews, Medical and Life Sciences ("TOP-GO").
- Cyriel Pennartz acquired a Collaborative Grant from the Cognition Spearhead Programme of the University of Amsterdam (PhD student fellowship).
- Cyriel Pennartz acquired a grant from the NWO Programme for Excellence 'Brain and Cognition´ together with Prof. Dr. P. R. Roelfsema, € 499.000.
- Cyriel Pennartz acquired a EU STREP grant: 'Goal-Leaders' together with a Consortium of investigators in Cognitive Science and Robotics (UvA share ~k€ 685).
- Cyriel Pennartz and Francesco Battaglia each acquired a grant from the Open Programme in the Earth & Life Sciences (NWO), for a PhD studentship and postdoc fellowship, respectively.
- Francesco Battaglia was appointed Associate Editor at Brain Research and Cyriel Pennartz functions as Associate Editor at the European Journal of Neuroscience.
- The Master Curriculum in Brain and Cognitive Sciences received a very good/excellent evaluation from the NVAO. In this curriculum, Battaglia is member of the teaching committee and Pennartz (co-)director of the track ´Cognitive Neuroscience´.

Research aims for the coming year

- We aim to disrupt memory consolidation and extra-hippocampal replay by electrical and optogenetic intervention of hippocampal processing in rats. The results will be used to develop novel methods for intervening with anxiety and PTSD-like disorders.
- The in vivo 2-photon imaging technique, combined with bulk labelling of neurons with Calcium-indicator dyes, will permit us to study multimodal interactions in the population dynamics of sensory neurons in the rat neocortex. Bulk labelling methods will be supplemented with genetically encoded Calcium dyes, e.g. GCamp-3. We further aim to study ensemble activity at high spatial resolution in a more evolved type of cortex, i.e. of ferrets.
- We aim to develop a dual visual task for rats that will allow scientists to establish whether rodents or ferrets have perceived a stimulus or not. Multi-area recordings are planned to examine ensemble interactions during visual perception.
- We aim to make further ensemble recordings from mutant mouse brains, yielding indications about the neural mechanisms of spatial memory, self-localisation, short- and long-term consolidation. Recordings from several genetically modified mouse lines will be completed (e.g. Arc & FMR-1 genes). Ensemble

recordings from mice with hippocampal NMDA-receptor deletions will be completed. This project will also be the test-bed for the development of a wireless electrophysiology recording system.

- We plan a new series of experiments investigating the interaction between the hippocampus and prefrontal cortex during sleep, by using Local Field Potential and Current Source Density Analysis methods.
- Using ensemble recording techniques applied to several neocortical and hippocampal recording areas simultaneously, we will study how information from the tactile and visual sensory modalities is integrated along the sensory neocortical-to-hippocampal hierarchy, using optogenetic techniques in combination with electrophysiology.
- A similar approach will be followed in a novel project on audio-visual integration applied to the problem of how the brain localises multimodal sources in the environment.
- Based on the newly developed behavioural protocol for studying the effects of stress hormones on decision-making and learning (place preference), we will conduct ensemble recordings from hippocampus and orbitofrontal cortex to examine how these hormones affect the neural mechanisms underlying the behavioural changes.
- New technological possibilities will be utilized to identify the cell types and intracellular correlates of a number of processes indicated above. These techniques range from optogenetics and in vivo 2-photon imaging to in vivo patch-clamp in the awake state. Particularly sub(spike) threshold intracellular phenomena resulting from multimodal interactions between sensory inputs will be studied.

Cellular and Systems Neurobiology

Chairholder: Prof.dr. W. J. Wadman

Dr. J. A. van Hooft	Assistant Professor
Dr. J. A. Gorter	Assistant Professor
Dr. T. R. Werkman	Assistant Professor
Dr. N. L. M. Cappaert	Assistant Professor

Introduction

Excitability is still the most prominent property of the nervous system. How ion-channels are organised and quantitatively balanced in the neuronal membrane, how they lead to neuron specific firing patterns and neuronal activity is modulated at different times scales (plasticity) belong to the most exciting questions in neuroscience. We approach them from a multidisciplinary angle. Neurons communicate with each other through a variety of synapses. To provide minimal functionality, neurons need to be combined in small circuits. New techniques allow us to slowly shift the focus of our research from the single cell to the (small) circuit level. Our research is organised around a few well defined topics in the realm of neuronal excitability. Our core approach is a functional electrophysiological one (from patch-clamping to in vivo). State-of-the-art optical techniques (Ca-imaging, Voltage Sensitive Dyes) and various multi-contact electrode recordings allow the analysis of population activity.

Research Highlights

The first of our three major research lines studies the fundamental properties of the 5-HT3 receptor and investigates its functional role in local circuits, development and behaviour. Molecular techniques produced mice in which the 5-HT3 receptor expressing neurons are labelled with GFP and can be studied efficiently. This has opened a wide range of possibilities to investigate the role of this receptor in functionally connected neurons and also its highly specific role in cortical column formation.

The second research line studies epilepsy e.g. seizure generation, epileptogenesis and pharmacoresistance. The latter topic we approach from two sides: a) (non-)penetration of drugs via the blood-brain-barrier and b) modification of drug targets, mainly sodium channels. These studies are of high clinical relevance and we strengthen them through side appointments at the Academic Hospital in Ghent and intense collaboration with the epilepsy center in Heemstede (SEIN). The therapeutic potential of deep brain stimulation is investigated in patients and in animal models.

The third research line concentrates on specific pharmacological modulation of neuronal circuits. We have a continuous collaboration with Solvay Pharmaceuticals in Weesp on the interactions of serotonin and dopamine in the Ventral Tegmental Area and the Substantia Nigra, two areas highly relevant for schizophrenia. Within the context of Top Institute Pharma we investigate the role of the endocannabinoids at the cellular and the circuit level in the PreFrontal Cortex (PFC).

Most of our experiments are supported by computer modelling, focusing on single cell excitability in relation to the direct chemical surrounding of the neuron as well as on the adaptive strategies for excitability that optimize the working range of active neurons. In the latter case we try to extrapolate the consequences of single cell strategies to larger neuronal networks. The combination of theoretical and experimental work has proven to be very fruitful in the scientific setting of SILS and the FNWI.

Other Highlights

On May 28th, Erwin van Vliet received the Meinardi Award for best thesis in epilepsy, 2007-2010. The prize is awarded by the National Dutch Epilepsy Foundation. The research for his thesis: *The role of the blood-brain barrier and multidrug*

transporters in pharmacoresistant epilepsy was performed in our group under the guidance of Jan Gorter and Wytse Wadman and financed by a grant from the Stichting Epilepsie Instellingen Nederland (SEIN, Heemstede).

A new grant awarded to Wytse Wadman from the Platform for alternatives in Animal Experimentation was started (Luuk van der Velden), with the aim of making tests for Anti-Epileptic Drugs more efficient and less dependent on laboratory animals. A new set-up based on a Multi Electrode Array (64-128 channels) was configured for that aim and successfully tested on slices from VTA and SN.

We contributed to a management book BREIN@WORK, relating fundamental properties of the brain to best management principles in human resource management. The book made it to a respectable second place in the Dutch management book of the year competition.
Jan Gorter acquired a new NEF project that will employ a PhD student and concentrate on the way inflammation underlies epileptogenesis.

Future Prospects

The coming year, most of our PhD students will finish their projects and round up results. The downfall of the Dutch pharma industry, with whom we have collaborated intensely and successfully over the last 10 years will require a reorientation of some of the research lines. The success of the collaboration with Philips Eindhoven, will lead to strengthening of the research on fundamental principles of Deep Brain Stimulation.
We have found a very successful synthesis between experiments and theory and were able to underpin many experimental studies by insightful computational modelling.
Unfortunately, to a large extent such a success builds on the expertise of only a very few temporary collaborators and is therefore volatile.

Structural and functional plasticity of the nervous system

Chairholder: Prof. dr. P.J. Lucassen

Dr. H. Krugers	Assistant Professor
Dr. C.P. Fitzsimons	Assistant Professor

Introduction

Group Lucassen/Krugers

We study structural and functional plasticity in the brain and focus on adult neurogenesis and synaptic plasticity in relation to stress, learning and memory and diseases like depression, epilepsy and dementia.

Current status

The past year, the group has gone through a transitional phase following the leave of Marian Joels and her group members to Utrecht. The remaining group of Lucassen and Krugers was expanded with VIDI laureate Fitzsimons, technician Meerhoff and assistant professor Korosi, as well as with several new PhD students who started their projects. Furthermore the research line on stress has shifted more to, in particular, early life stress, and the subsequent consequences for learning and memory and the development of (psycho)pathology later in life. With Fitzsimons joining the group, more molecular and viral tools will be available that will also allow us to focus on molecular mechanisms of such stressors like epigenetics and microRNA regulation, while Korosi will strengthen behavioural, epigenetic and early life stress expertise.

In 2010, the teaching and management load has further increased due to the strong rise in bachelor student numbers and the introduction of a newly developed master curriculum, also in terms of committee work. As such, the senior members face increasing challenges in dividing their time between teaching, management and research in the very competitive and rapidly developing research fields of neurogenesis and AMPA receptor biology. Despite this, the group has kept up a very good output in 2010 and managed to publish 18 high quality papers this year, a.o. in J. Neuroscience and Nature Rev Neurosci.

Research Highlights

We tested if severely adverse early-life stress reduces structural and functional plasticity in adult life. After maternal deprivation at postnatal day 3, reduced levels of adult hippocampal neurogenesis and an altered dendritic tree organisation were found in adult animals. These structural changes were not only paralleled by impaired learning of a spatial learning task, but also by improvements in network properties and emotional learning under high-stress conditions. Hence, adversity early on in life is not always 'bad', but can even improve emotional forms of memory and thereby prepare the organism to perform optimally under stressful conditions in adulthood (Oomen et al., J Neurosci, 2010, Oomen et al., Psychophamacology, 2011).

Other highlights

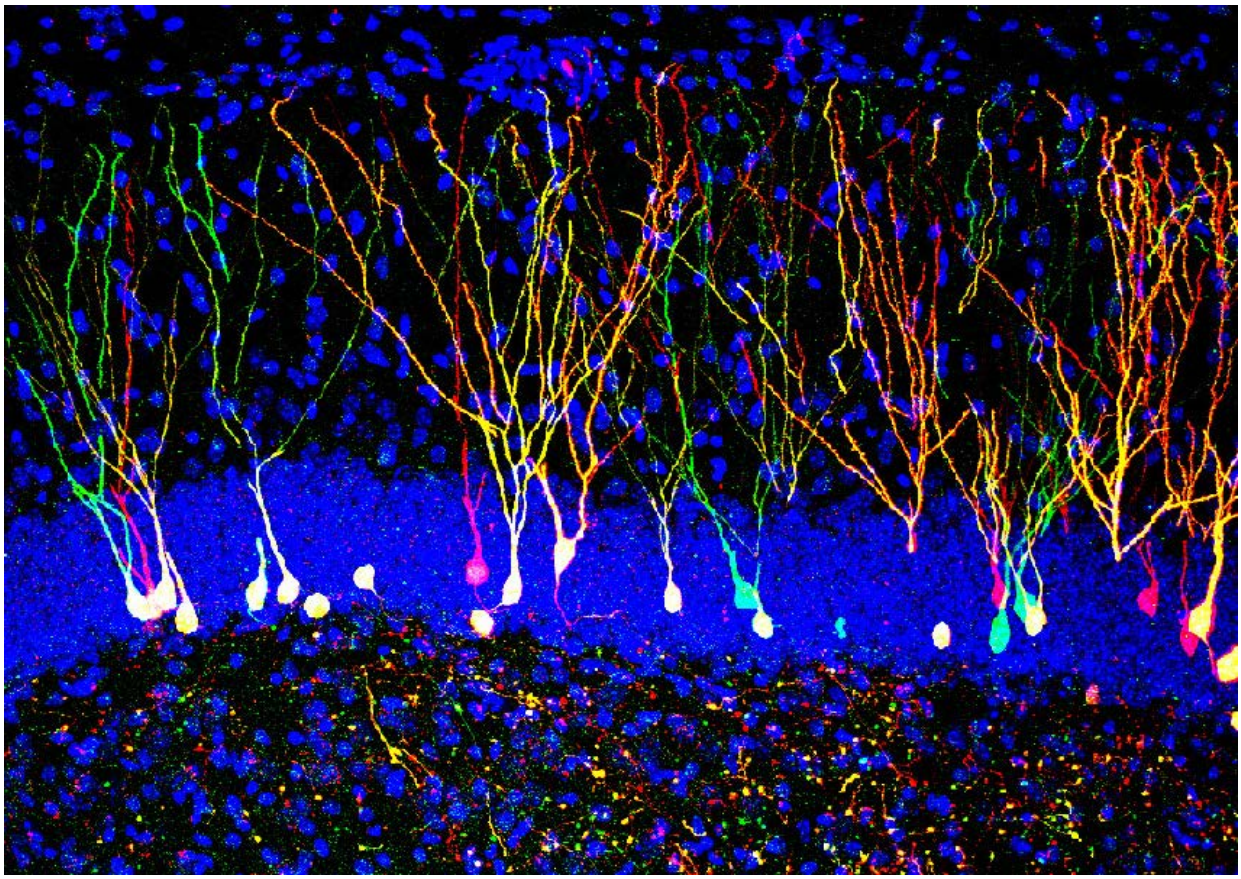
The group has improved its visibility, and the visibility of SILS/UVA, by organising the International NEURAD Alzheimer meeting (PL) in Amsterdam, as well as several master classes and sessions at scientific meetings (ENP, HSN publieksdag, ECNP, FENS, ISAO workshop), and by membership of the boards of ALW-NWO (HK), the Neurofederation (HK, board secretary) and the International Alzheimer Society ISAO (chairman of the Scientific Advisory Board, PJL). Group members were also successful in obtaining external funding from NWO (CF, HK, PL), the Alzheimer (ISAO to HK) and Parkinson Foundation (IPF to PL) and industry Corcept (PL with Joels). Group members received numerous invitations to give lectures or write papers and chapters and to act as invited reviewer for major journals like J Neuroscience, Biological Psychiatry, PNAS, Nature and Science.

Research aims for the coming years

- To further develop our research line into the consequences of stress during early life for

structural and synaptic plasticity, AMPA receptor dynamics and cognition at adult age.
- To extend these lines into models of diseases like depression, anxiety, epilepsia and dementia.
- To extend the research on neurogenesis in rodent models to other brain areas like the amygdala and cortex and also in a translational perspective to human brain.
- To develop translational approaches to monitor and measure neurogenesis in the live human brain using MRS spectroscopy in relation to development and depression.

To incorporate and develop tools to manipulate adult neurogenesis in vivo using molecular and viral tools.
- To increase our understanding of the molecular mechanisms underlying stress-mediated regulation of learning and memory through e.g. AMPA receptor trafficking and spinogenesis.
- To determine how proteins that are critically involved in dementia regulate synaptic function and cognition.



Adult neurogenesis as identified by retroviral mediated labeling of newborn neurons (white) in the adult hippocampus (blue cells). Picture: Paul Lucassen & Boldizsar Cze

Research Programme Life Science Technologies

Mass Spectrometry of Biomacromolecules

Chairholder: Prof. dr. C.G. de Koster

Dr. L. de Jong	Associate Professor
Dr. L.J. de Koning	Assistant Professor

Introduction

In the context of the UVA priority area Systems Biology, Mass Spectrometry of Biomacromolecules focuses on three research themes that adhere to the study of cellular response to external signals. (1) We study post-transcriptional regulation of gene expression by quantitatively analysing protein concentrations, synthesis and degradation rates and mapping post-translational modifications. (2) We develop new analytical strategies for the experimental evaluation of models of the 3-D structure of protein complexes. (3) We aim at insight in adaptation of the cell surface proteome of fungi and bacteria. SILS-MS is developing advanced and innovative, mass spectrometry-based proteomics technology that is designed for these research areas. Our technology is not confined to the field of molecular systems biology and is widely applicable to biology. Here, we have long term collaborations with the SILS plant groups where we study fungal pathogen – plant interaction and identify target proteins upon stress.

Research Highlights

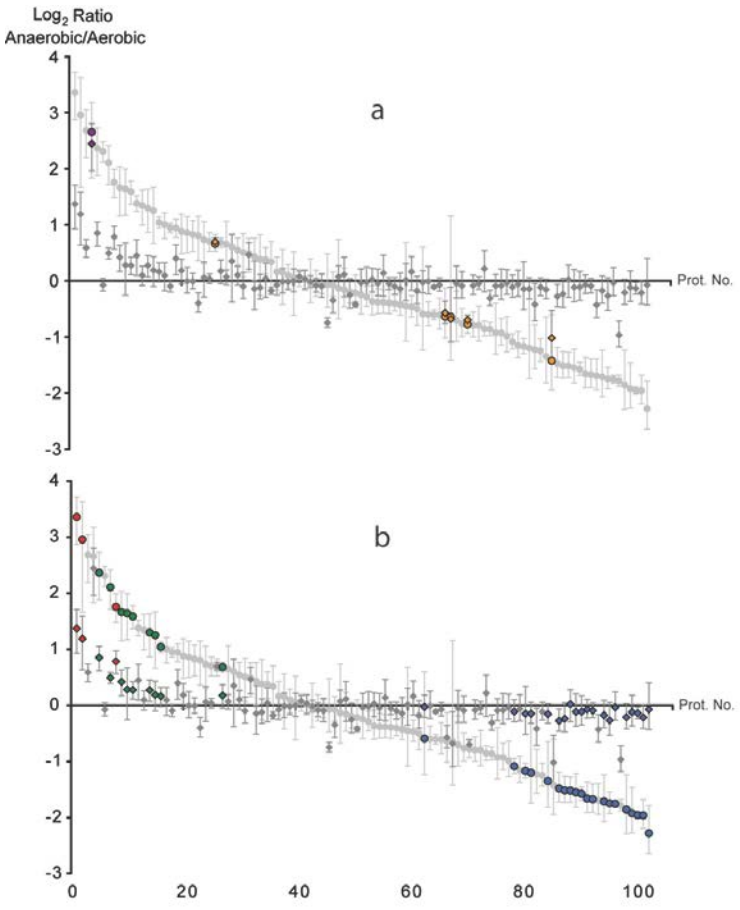
Enzyme reprofiling in bacteria during adaptation from one environmental condition to another may be regulated by both transcription and translation. However, little is known about the contribution of translational regulation. Recently, we have developed a pulse labelling method using the methionine analog azidohomoalanine to determine the relative amounts of proteins synthesised by *Escherichia coli* in a brief time frame upon a change in environmental conditions. We extended our analytical strategy. The improved method entails measuring changes in total protein levels on the same time scale as new protein synthesis for the first time. This allows identification of stable and labile proteins and demonstrates that altered levels of most newly synthesised proteins are the result of a change in translation rate rather than degradation rate. With this extended strategy, average relative translation rates of 10 minutes immediately after a switch from aerobiosis to anaerobiosis were determined. The majority of proteins with increased synthesis rates upon an anaerobic switch are involved in glycolysis and pathways aimed at preventing glycolysis grind to a halt by a cellular redox imbalance. Our method can be used to compare relative translation rates with relative mRNA levels at the same time. Discrepancies between these parameters may reveal genes whose expression is regulated by translation rather than by transcription. This may help unravel molecular mechanism underlying changes in translation rates, e.g. mediated by small regulatory RNAs.

Other Highlights

We organised an international three-day course *Fundamentals of Mass Spectrometry and Proteomics* for the participants of the EU Marie Curie Consortium FINSysB at Science Park Amsterdam from October 4th to October 6th 2010.

Research aims for the coming year

Focal points in our MS research programme are as mentioned above (1) post-transcriptional regulation of gene expression, (2) systematic analysis of protein-protein interactions, and (3) proteomics at the cell surface. (1) In 2011, we will finalise our method development for estimation of protein degradation rates from azhal pulse labelling MS data sets. We will move in this research line to the study of post translational modifications that affect function and activity of proteins. Oxidation affects the activity of many proteins and their loss by degradation and aggregation. The latter may lead to cellular dysfunction and eventual death. Protein oxidation by reactive oxidative species comprises a plethora of reactions. We will map in vivo protein modification caused by oxidative stress imposed on cells and correlate this map with biological function and dysfunction. We will start with the reactivity of hydroxyl radicals towards proteins in the mitochondrion. Another important reaction in this organelle is carbonylation of proteins. In programme (2) we will map interaction sites of initiation and elongation factors that modulate the activity of RNA polymerase and we will quantitate cross-links formed during initiation and elongation, in an effort to detect conformational changes. (3) The MS group will continue to explore the question how mass spectrometry, in combination with novel purification strategies and bioinformatics tools, can provide detailed quantitative structural and functional information about proteins at the interface between the cell and its external environment. In the framework of the EC FINSysB project, we will focus on the quantitative cell wall protein composition of *Candida albicans* to identify new leads for novel anti-*Candida* vaccines, drugs and diagnostic markers. In collaboration with Prof. Brul, we will carry out functional characterisation of spore coat proteins of *B. subtilus.* We will continue the productive collaborations with the groups of the SILS-plant programme, directed to characterisation of proteins secreted by the cell upon host-pathogen interactions, and with our external national and international partners.



Changes in protein synthesis by *Escherichia coli* compared with changes in protein levels upon onset of anaerobiosis. *Light gray* or *coloured circles*, relative change of newly synthesised proteins; *dark gray* or *coloured diamonds* at the same position on the *x axis* as a *circle* are relative total protein levels of the same protein 10 min after the switch to anaerobiosis. Proteins are ordered from most induced to most repressed synthesis. In *a*, proteins having a *high* turnover rate are marked, namely GrcA (*purple circle* and *diamond*) and ClpA, KatG, AhpC, MetN, and AhpF (*orange circles* and *diamonds*). In *b*, coloured symbols are used to represent proteins with a *low* turnover rate in the same data set. *Red circles* and *diamonds*, proteins involved in anaerobic respiration and mixed acid fermentation; *green circles* and *diamonds*, glycolysis; *blue circles* and *diamonds*, ribosomal proteins. *Prot.*, protein.

Biosystems Data Analysis

Chairholder: Prof. dr. A.K. Smilde

Dr. H.C.J. Hoefsloot	Associate Professor
Dr. J.A. Westerhuis	Assistant Professor
Prof. dr. A.H.C. van Kampen	Special Chair

Introduction

General goal

Developing and validating methods for organising, summarising and visualising complex biological data.

The research is divided in three connected themes: Semantic Biosystems, Data Fusion and Networks & Dynamics. We apply our methods in diverse areas of systems biology focusing mainly on microbiology, nutrition and medical biology.

Semantic Biosystems (Antoine van Kampen)

Well-structured, accessible and integrated information is crucial for disciplines like genomics and systems biology. To support these disciplines, we develop novel information management approaches based on cutting-edge Semantic Web standards in a framework that allows the construction of high quality domain-specific knowledge bases.

Data Fusion (Johan Westerhuis)

To understand the functionality of complex biological systems, different types of measurements have to be combined with systems information stored in a knowledge base. We develop data analysis methods that are able to find biologically relevant patterns in these data that on the one hand match the systems information and on the other hand generate new insights.

Networks & Dynamics (Huub Hoefsloot)

In a biological system molecules interact. These interactions, the network, causes the system to change over time. We develop methods to reverse engineer networks from time-resolved functional genomics data. The networks can be metabolic networks, protein-protein interaction networks, gene-regulatory networks or association networks.

Research highlights

General

We have been able to fill all vacant positions in the group and have established new international collaborations, e.g. with Aarhus University in the area of Nutrition and Production Physiology; with University College Dublin in the area of multicompartment modelling; with Oxford University in the area of BioPax and Citation Typing Ontology. This gives us the opportunity to obtain data sets and validate our methods on real-life problems.

Semantic Biosystems

Interest in knowledge publication, management and integration is growing rapidly, and the BioExpert project is ideally placed to take advantage of this. We have accumulated a great deal of experience in the application of Semantic Web technologies, and methodologies that support the creation and publication of new knowledge base content. The Peroxisome Knowledge Base has a new portal on the web (www.peroxisomekb.nl), which has allowed us to publish the knowledge base content already captured in concept maps in an open, machine-readable way, known as Linked Data. The peroxisome vocabulary that forms the core of the knowledge base has been significantly improved and extended and now includes over 1600 peroxisome related concepts, with ~1000 of these linked to a public resource and many now having definitions and several labels. The knowledge base also contains over 4000 peroxisome related publications as RDF converted from MedLine. We have used the vocabulary to 'text-mine' these publications to identify peroxisomal concepts mentioned in the titles and abstracts, giving over 60,000 links between the vocabulary and the publications. In order to support ongoing work on the

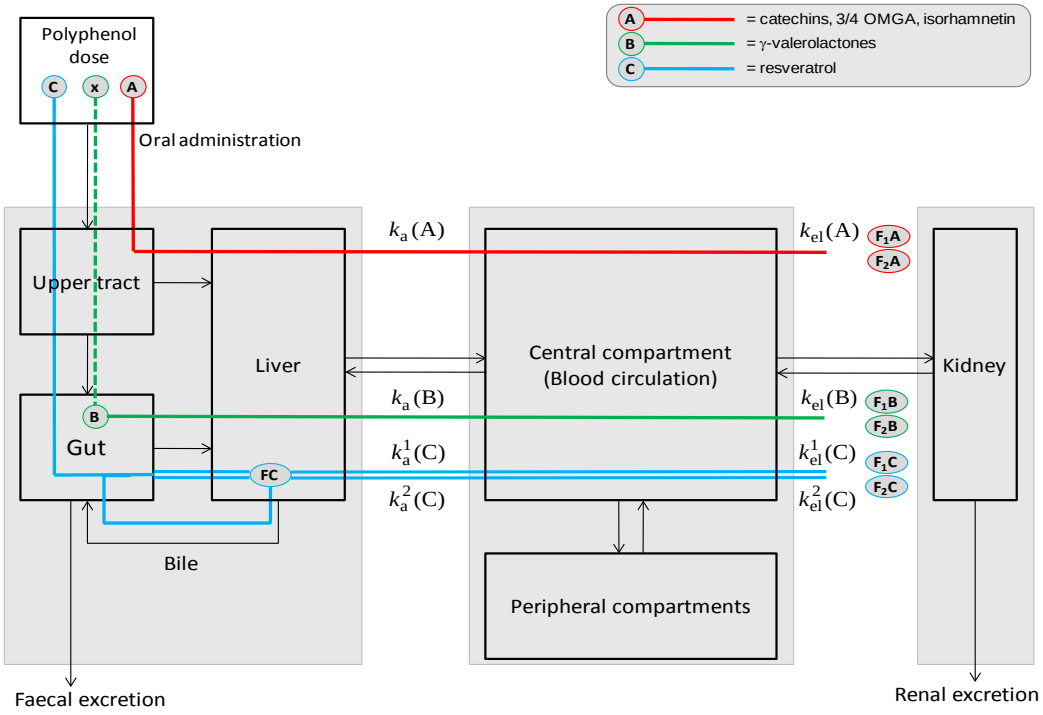
vocabulary, and further involve experts from the field, we have developed a new application for editing SKOS vocabularies that are in an RDF triplestore. We started research to implement a polyphenol degradation knowledgebase and to integrate this with grey statistical modelling. Collaboration with Peter Barth and Bwee-Tien Poll-Thé (Pediatric Neurology, AMC) is yielding a very detailed description of concepts related to Zellweger Syndrome, on which he is a leading figure. We have also begun collaborations with partners in NCSB, TNO and VU to construct new knowledge bases on Metabolic Syndrome and Yeast Glycolysis. Collaborations are also ongoing to develop and deploy standards for knowledge publication (nanopublications), standards for pathway data on the Semantic Web (BioPAX) and standards for metadata about publications (Citation Typing Ontology, CiTO).

Data Fusion

Repeatability of metabolomics measurements reveals that each metabolite may have a different measurement error that depends on its concentration. A new measurement error model was developed that also takes into account the correlation between measurement errors of different metabolites. Biological variation between human individuals gives rise to two data analysis problems. Small treatment effects cannot be observed and treatment effects may be different for the individuals. A new data analysis method (MLPLSDA) was introduced that is much better able to find the individual treatment effects than conventional methods. Johan Westerhuis received the EAS Award for Outstanding Achievements in Chemometrics for his contributions to the field of chemometrics.

Research Highlight

In a recent PNAS paper we described the metabolic faith of polyphenols in humans. The figure below shows a compartmental model depicting the nutrikinetic processes of phenolic compounds across the human system. Three nutrikinetic processes are illustrated; (A) fast systemic absorption of phenolic compounds via the upper digestive system, (B) delayed and slow systemic absorption of gut-mediated metabolites derived from phenolic components (x), and (C) biphasic absorption of resveratrol due to enterohepatic cycling between liver and intestine. Constants $k_a(A)$, $k_a(B)$, and $k_a(C)$ are the absorption rate constants; $k_{el}(A)$, $k_{el}(B)$, and $k_{el}(C)$ are the elimination rate constants; F_1 and F_2 are the absorbed fractions of native and conjugated compounds, and FC is the fraction of resveratrol absorbed in the bile.



Networks & Dynamics
In 2010, a paper on the reverse engineering of metabolic networks is accepted. It showed that it is difficult to reconstruct metabolic nets because the time constants involved in metabolic reactions vary over a large range. To capture the dynamics of the network fast sampling is necessary to capture the fast reactions. This sampling turned out to be faster than most systems for metabolomics are capable of. For endocrine regulation, association networks were built from time-resolved hormonal data (collaboration with the LUMC). These regulatory networks show differences between control and diseased persons, and between patients before and after treatment in concise and biologically interpretable way.

Research aims for the coming year

General
Bringing together the fields of biostatistics and bioinformatics.

Semantic Biosystems
Our new collaborations with partners within NCSB, TNO and Vrije Universiteit present the opportunity to employ the technologies and methodologies for constructing knowledge bases in different areas. We will develop knowledge bases and new tools that support the needs of researchers in these organisations wishing to capture and use their expert knowledge. Our knowledge base architecture will be extended in order to support the tasks of pathway modelling (VU) and the interpretation and annotation of datasets derived from system-level experimentation (TNO). The existing PeroxisomeKB will be extended and important as an established Semantic Web framework in which new ideas for information management can be validated. We expect first results with the integration using prior knowledge, from the polyphenol knowledgebase, in grey statistical modelling.

Data Fusion
In the following years the focus will be on the analysis of functional genomics data obtained from challenge tests. In such tests the individual is brought out of homeostasis and its resilience is observed. The goal is to develop data analysis methodology that can describe data obtained from such tests for improved mechanistic information and to provide better prediction of the health status of individuals.

Networks & Dynamics
In the next few years we are going to develop tools to analyse the interactions of bio-molecules and the changes of these interactions over time. For this we will use and adapt concepts for the analysis of covariation- and correlation matrices. Especially the changes in covariance and correlation over time will have our attention. A first paper on this has already been submitted. Together with our collaborators at the Amsterdam Free University we will estimate protein protein interaction networks in the synaps. The data is measured using immuno precipitation experiments. Methods will be developed to extract information on protein complexes in the synaps.

Micro Array Department and Integrative Bioinformatics Unit

Group leader: Dr. T.M. Breit

Dr. Ir. R.A. Wittink Project management "wet-lab"
Drs. O. Bruning Project management "dry-lab"

Introduction

MicroArray Department (MAD) & Integrative Bioinformatics Unit (IBU):
Microarray technology is a well-established tool for genome-wide gene expression, i.e. transcriptomics studies. The ultimate goal of a microarray experiment is to simultaneously investigate the expression of all genes of a specific organism, in a cell type, during specific growth or stress conditions. This enables the study of complex cellular mechanisms or identification and use of biomarkers. Transcriptomics biomarkers are genes whose expression profile can be used for diagnostic purposes or to monitor and predict cellular processes. Recently, innovative next-generation sequencing technologies have also become available for gene-expression analysis. Because transcriptomics experiments produce a vast amount of data, extensive bioinformatics infrastructure, methods and expertise are needed to cope with these data effectively. Bioinformatics for transcriptomics comprises: data-handling (storage and exchange), data-preprocessing (normalisation and validation), data-analysis (clustering, biomarker selection, etc.), and e-infra (high-performance computing, grid, cloud).
The MAD-IBU consists of a microarray technology section (Wet-lab) with ~5 specialists that provides transcriptomics service and support and performs microarray and next-gen. sequencing technology R&D; a transcriptomics data-analysis section (Dry-lab) with ~9 bioinformaticians and informaticians that provides transcriptomics data analysis service and support, performs bioinformatics R&D, and builds e-infra. Together, the MAD operates as a transcriptomics technology and bioinformatics expertise centre and core facility for UvA scientists, as well as external academic and industrial customers.
The focus of the Wet-lab R&D is to improve the microarray technology for transcriptomics with a strong focus on array controls and sample size reduction. We aim to eventually analyse various types of single cells by microarray technology such as (un)fertilised eggs. The focus of the Dry-lab is on the bioinformatics and e-bioscience methods, tools and infrastructure necessary to perform advanced transcriptomics data-analysis starting from array design to publication. Another important focal point for the whole group is design-for-experimentation. Performing well-designed range-finding experiments should elucidate the role of time and space in transcriptomics experiments. To this end, MAD-IBU participates in six nation-wide projects: *BioRange*, a NBIC bioinformatics research project; *BioAssist*, a NBIC bioinformatics support programme; *Virtual Lab for e-Science* (VL-e); e-Science Center (eSR); and e-BioGrid -BiG Grid-, *Virtual Lab for Plant Breeding* (VLPB), all four being Dutch Bsik or NWO e-science projects in the field of e-infrastructure and methods.

Research Highlights

The Wet & Dry-lab:
Introduction of new high-throughput Affymetrix microarray platform: GeneTitan.
First major microRNA project with AMC.
Established a strategic collaboration with the Center of reproductive medicine at the AMC.
Started to build the analysis pipeline for next-generation sequencing data.
Start of the first 3 PhD students at the MAD.
Performed over 70 collaborative experiments for biologists in 2010 alone.

Other highlights

The whole group further strengthened the strategic collaborations with several external research organisations: Laboratory for Health Protection Research, RIVM, (Bilthoven); Medical Microbiology, UMC (Utrecht); ACTA, VU-AMC (Amsterdam); Molecular Cell biology, UL, (Leiden); Center of reproductive medicine, AMC, Amsterdam.

Research aims for the coming year

- To develop ultimate unbiased microarray gene-expression and CGH protocols.
- To analyse maternal RNAs in unfertilised Zebrafish and human eggs.
- To analyse the transcriptomics of the earliest stages of Zebrafish and human embryogenesis.
- To analyse a hallmark time-axis microarray experiment on Zebrafish.
- To perform several range-finding experiments in the context of design-for-experimentation.
- To extend the Problem-Solving Environment (PSE) for microarray data analysis and interpretation.
- To become a central player in the national e-bioscience domain, such as the UvA zwaartepunt e-science and the e-Science Research Centre.
- To file at least 1 patent on microarray technology innovations.
- To write > 15 (collaborative) research articles.

Management

Finance

The integrated results for 2010 show an operating profit of 143 k€ where a negative result of 859 k€ was budgeted. This is partially due to delayed employment of new personnel.

Year	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**
University funding	5838	6131	7364	8987	7577	13234	12795	13848	13580	14561
External funding	3852	3883	4474	6167	4515	4701	4952	5489	5084	4736
total revenues	9690	10014	11838	15154	12092	17935	17747	19337	18645	19297
Personnel costs	7096	7465	8919	9626	9122	12816	13918	14448	11191	10342
Bench fees**	2236	2450	3310	4989	2729	5362	4138	5240	7795	8812
total costs	9332	9915	12229	14614	11851	18178	18056	19688	18986	19154
result	**358**	**99**	**-391**	**540**	**241**	**-243**	**-309**	**-351**	**-342**	**143**

Table 1: Representation of revenues and costs of the Swammerdam Institute for Life Sciences, in k€, for the years 2001-2010. In 2006, the university changed to a new financial system in which budgets were increased and full costs were calculated.
** as of 2009, costs that were included in “personnel costs” were transferred to “bench fees”

Revenues and costs over 2010 can not be compared directly with previous years and higher numbers in the “funding” part not necessarily reflect more money for research. This is due to ongoing changes in the financial methodologies used by the UvA. Therefore, to assess the capacity of the institute the number of employees may provide a better insight.

Year	**2008**	**2009**	**2010**
FTE university funded	95.6	90.6	90.6
FTE (NWO/FOM funded)	24.1	20.0	33.3
FTE (EU, contracts)	42.5	38.1	37.3
FTE (scholarships)	1	11	10
Total number of FTE*	**163.1**	**159.7**	**171.6**

Total number of employees	**172**	**167**	**180**

Table 2: number of FTE and employees on December 31st of each year.

Funding

The funding system of Dutch universities distinguishes three different kinds of funding resources. These are referred to as so called "funding sources" and are numbered one to three. Resources originating from the university itself are referred to as the first funding source. External funding is divided into funding from the Netherlands Organisation for Scientific Research (second funding source) and money originating from all other resources such as EU and contract research (third funding source).

	2003	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**
Revenues	7793	8987	7577	13234	12795	13848	13580	14561
Costs	8291	8902	7357	13580	13259	14115	13845	14068
Result	-498	85	220	-346	-464	-306	-265	493

Table 3: representation of income and costs in the 1st funding source, in k€, for the years 2003-2010.

	2003	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**
Revenues	2279	2303	2160	2032	2299	2434	1821	1884
Costs	2279	2303	2160	2048	2226	2436	1713	2195
Result	0	0	0	-16	73	-2	108	-311

Table 4: representation of income and costs in the 2nd funding source, in k€, for the years 2003-2010.

	2003	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**
Revenues	1766	3864	2355	2669	2653	3055	3244	2851
Costs	1659	3409	2334	2550	2571	3097	3429	2891
Result	107	455	21	119	82	-42	-185	-40

Table 5: representation of income and costs in the 3rd funding source, in k€, for the years 2003-2010.

Table 4 shows an exceptional negative result of -311 k€ in the 2nd funding source where a result of ~0 is expected. This is caused by a change in the financial methodologies related to two KNAW (Royal Dutch Academy of Arts and Sciences). The funds for these projects were received in previous years and were sufficient.

Personnel

The university aims at a more equal division of males and females in the staff at all levels. On December 31st, 2010 the PhD student male: female ratio was 41:59. At the post doctoral level this was 83:17. Of the assistant professors 71% was male. Age-wise our staff is spread over the full range from starting PhD, to people who are (close to) retiring.

Infrastructure

In 2010, the entire Swammerdam Institute for Life Sciences was located in the new building of the faculty. Positive aspects of the new infrastructure are the brand new labs in a beautiful building.

Appendix 1

Research Programme **Systems Biology of the Living Cell**

Molecular Microbial Physiology

Patent application

M. Bekker, M.J. Teixeira de Mattos, K.J. Hellingwerf: Production of L-lactic acid by photofermetation. P6030715PCT

Academic publications

Anemaet, I.G., Bekker, M. & Hellingwerf, K.J. (2010). Algal photosynthesis as the primary driver for a sustainable development in energy, feed, and food production. *Marine Biotechnology, 12*(6), 619-629.

Maischberger, T., Mierau, I., Peterbauer, C.K., Hugenholtz, J. & Haltrich, D. (2010). High-level expression of Lactobacillus beta-galactosidases in Lactococcus lactis using the food-grade, nisin-controlled expression system NICE. *Journal of Agricultural and Food Chemistry, 58*(4), 2279-2287.

LeBlanc, J.G., Sybesma, W., Starrenburg, M., Sesma, F., Vos, W.M. de, Savoy de Giori, G. & Hugenholtz, J. (2010). Supplementation with engineered Lactococcus lactis improves the folate status in deficient rats. *NUTRITION, 26*(7-8), 835-841.

LeBlanc, J.G., Sinderen, D. van, Hugenholtz, J., Piard, J.C., Sesma, F. & Savoy de Giori, G. (2010). Risk assessment of genetically modified lactic acid bacteria using the concept of substantial equivalence. *Current Microbiology, 61*(6), 590-595.

Goffin, P., Bunt, B. van de, Giovane, M., Leveau, J.H.J., Höppener-Ogawa, S., Teusink, B. & Hugenholtz, J. (2010). Understanding the physiology of Lactobacillus plantarum at zero growth. *Molecular Systems Biology, 6*, 413.

Eunen, K. van, Bouwman, J., Daran-Lapujade, P., Postmus, J., Canelas, A.B., Mensonides, F.I.C., Orij, R., Tuzun, I., Brink, J. van den, Smits, G.J., Gulik, W.M. van, Brul, S., Heijnen, J.J., Winde, J.H. de, Teixeira De Mattos, M.J., Kettner, C., Nielsen, J., Westerhoff, H.V. & Bakker, B.M. (2010). Measuring enzyme activities under standardized in vivo-like conditions for systems biology. *The FEBS Journal, 277*(3), 749-760.

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Ávila-Pérez, M., Steen, J.B. van der, Kort, R. & Hellingwerf, K.J. (2010). Red light activates the sigma(B)-mediated general stress response of Bacillus subtilis via the energy branch of the upstream signaling cascade. *Journal of Bacteriology, 192*(3), 755-762.

Metz, S., Hendriks, J., Jager, A., Hellingwerf, K. & Klug, G. (2010). In vivo effects on photosynthesis gene expression of base pair exchanges in the gene encoding the light-responsive BLUF domain of AppA in Rhodobacter sphaeroides. *Photochem.Photobiol., 86*(4), 882-889.

Fiedler, T., Bekker, M., Jonsson, M., Mehmeti, I., Pritzschke, A., Siemens, N., Nes, I., Hugenholtz, J. & Kreikemeyer, B. (2011). Characterization of three lactic acid bacteria and their isogenic ldh deletion mutants shows optimization for Y(ATP) (cell mass produced per mole of ATP) at their physiological pHs. *Applied and Environmental Microbiology, 77*(2), 612-617.

Membership editorial board

Teixeira De Mattos, M.J. (Ed.). (2010). FEMS Yeast Res..

Invited lectures

Hugenholtz, J. (2010, September 10). *Fermentation for natural enrichment of foods.* Zurich, Switzerland, ETH Zurich.

Hellingwerf, K.J. (2010, December 14). *Biophysics and Biochemisty of Photo-perception.* Amsterdam, Free University, Dr.R.Frese.

Hellingwerf, K.J. (2010, November 15). *The molecular basis of blue-light sensing in bacteria.* Karlsruhe, Germany, Botanical Inst.of the Karlsruhe Inst. of Technology.

Hellingwerf, K.J. (2010, November 12). *Biofuel production with Cyanobacteria.* Mikulov, CZ, Workshop Virtual photobioreactor: Cyanobacterium in silico.

Hellingwerf, K.J. (2010, October 18). *New ways to convert solar energy, H2O and CO2 into biofuel.* Buenos Aires, Argentina, XIIth Annual Meeting Argentinian Soc.for Microbiology.

Hellingwerf, K.J. (2010, September 05). *On the mechanism of signal transduction in the light-activated general stress response in Bacillus subtilis.* Barcelona, Spain, ESF Research Conference: BacNet/10.

Hellingwerf, K.J. (2010, June 13). *Biofuel production with Cyanobacteria using the Photanol approach.* Lake Arrowhead, USA, 10th Cyanobacterial Molecular Biology Workshop.

Hellingwerf, K.J. (2010, April 21). *The role of the protein in the isomerization reaction of photoactive yellow protein.* Il Ciocco, Italy, Gordon Conference on Photosensory Receptors and Signal Transduction.

Hellingwerf, K.J. (2010, April 21). *Biophysical methods as applied to photosense.* Il Ciocco, Italy, Gordon Conference on Photosensory Receptors and Signal Transduction.

Hellingwerf, K.J. (2010, March 24). *Systems biology of oxygenic photosynthesis.* Amsterdam, the Netherlands, NISB minisymposium.

Hugenholtz, J. (2010, October 20). *Fermentation for increased health benefits of beverages.* Davis,California, USA, University of Davis.

Hugenholtz, J. (2010, June 08). *SysMO-LAB1.* Noordwijkerhout, the Netherlands, Meeting SysMO-LAB.

Teixeira de Mattos, MJ (2010, January 8). Lecture on "The energetics of microbial growth and the costs of adaptation" Advanced Course on Biotechnology. Techn. University of Delft. Hosts: Profs S. Heijnen and J. Pronk

Teixeira de Mattos, MJ (June, 2010). Lecture on "From idea to spin-off: using engineered cyanobacteria for clean productions" Honours program, UvA **.**

Teixeira de Mattos, MJ (June, 14, 2010). Lecture on "Sustainable production of chemicals by engineered cyanobacteria" Department of Biophysics, Free University of Amsterdam, host: Prof v Grondelle)

Teixeira de Mattos, MJ (October, 2010). Lecture on "Biofuel production by engineered cyanobacteria" University of Delft

Teixeira de Mattos, MJ (November, 25-26, 2010). The Protein Summit, Bridge2food, Amsterdam: The real future: making meat from single cells.

Molecular Biology and Microbial Food Safety

PhD Thesis

Orij, P.J. (2010, November 18). *On the intracellular pH of baker's yeast.* UvA Universiteit van Amsterdam (168 pag.). Prom./coprom.: prof.dr. S. Brul & dr. G.J. Smits.

Patent application

Brul, S., Waal, S.V. van der, Soet, J.J. de & Sluis, L.W.M. van der (18-02-2010). Disinfectant composition and its use in dental treatment. no P6028544US.

Academic publications

Eunen, K. van, Bouwman, J., Daran-Lapujade, P., Postmus, J., Canelas, A.B., Mensonides, F.I.C., Orij, R., Tuzun, I., Brink, J. van den, Smits, G.J., Gulik, W.M. van, Brul, S., Heijnen, J.J., Winde, J.H. de, Teixeira De Mattos, M.J., Kettner, C., Nielsen, J., Westerhoff, H.V. & Bakker, B.M. (2010). Measuring enzyme activities under standardized in vivo-like conditions for systems biology. *The FEBS Journal, 277*(3), 749-760.

Klis, F.M., Brul, S. & Groot, P.W.J. de (2010). Covalently linked wall proteins in ascomycetous fungi. *Yeast, 27*(8), 489-493.

Havelaar, A.H., Brul, S., Jong, A. de, Jonge, R. de, Zwietering, M.H. & Kuile, B.H. ter (2010). Future challenges to microbial food safety. *International Journal of Food Microbiology, 139*(S1), S79-S94.

Zuijlen, A. van, Periago, P.M., Amézquita, A., Palop, A., Brul, S. & Fernández, P.S. (2010). Characterization of Bacillus sporothermodurans IC4

spores; putative indicator microorganism for optimisation of thermal processes in food sterilisation. *Food research international, 43*(7), 1895-1901.

Sorgo, A.G., Heilmann, C.J., Dekker, H.L., Brul, S., Koster, C.G. de & Klis, F.M. (2010). Mass spectrometric analysis of the secretome of Candida albicans. *Yeast, 27*(8), 661-672.

Zakrzewska, A., Boorsma, A., Beek, A. ter, Hageman, J.A., Westerhuis, J.A., Hellingwerf, K.J., Brul, S., Klis, F.M. & Smits, G.J. (2010). Comparative analysis of transcriptome and fitness profiles reveals general and condition-specific cellular functions involved in adaptation to environmental change in Saccharomyces cerevisiae. *Omics, 14*(5), 603-614.

Christoffels, V.M., Smits, G.J., Kispert, A. & Moorman, A.F.M. (2010). Development of the pacemaker tissues of the heart. *Circulation Research, 106*(2), 240-254.

Backhaus, K., Heilmann, C.J., Sorgo, A.G., Purschke, G., Koster, C.G. de, Klis, F.M. & Heinisch, J.J. (2010). A systematic study of the cell wall composition of Kluyveromyces lactis. *Yeast, 27*(8), 647-660.

Boer, A.D. de, Groot, P.W.J. de, Weindl, G., Schaller, M., Riedel, D., Diez-Orejas, R., Klis, F.M., Koster, C.G. de, Dekker, H.L., Gross, U., Bader, O. & Weig, M. (2010). The Candida albicans cell wall protein Rhd3/Pga29 is abundant in the yeast form and contributes to virulence. *Yeast, 27*(8), 611-624.

Young, B.P., Shin, J.J.H., Orij, R., Chao, J.T., Li, S.C., Guan, X.L., Khong, A., Jan, E., Wenk, M.R., Prinz, W.A., Smits, G.J. & Loewen, C.J.R. (2010). Phosphatidic acid is a pH biosensor that links membrane biogenesis to metabolism. *Science, 329* (5995), 1085-1088.

Non refereed publication

Zuijlen, A.C.M. van, Oomes, S.J.C.M., Vos, P. & Brul, S. (2009). Detecting bacterial spores in soup manufacturing. *New food*, 3, 21-24.

Book Chapter

Brul, S., Fratamico, P.M. & McMeekin, T.A. (Eds.). (2010). *Tracing pathogens in the food chain* (Woodhead Publishing series in food science, technology and nutrition, 196). Oxford: Woodhead.

Invited lectures

Klis, F.M. (2010, October 06). *Mass spectrometric quantitation of the adaptations in the wall proteome of Candida albicans in response to ambient pH.* Amsterdam, the Netherlands, 4th FINSysN Research Skills Training Workshop.

Brul, S. (2010, May 01). *Towards Modelling of heterogeneity in Bacillus subtilis spore germination and outgrowth.* Cortona, Italy, European Spore Conference.

Membership Editorial board

Brul, S. (Ed.). (2010). *Innovative Food Science and Emerging Technologies*.

Brul, S. (Ed.). (2010). *Food Microbiology*.

Klis, F.M. (Ed.). (2010). *Eukaryotic Cell*.

Klis, F.M. (Ed.). (2010). *FEMS Yeast Research*.

Klis, F.M. (Ed.). (2010). *Eukaryotic Cell*.

Klis, F.M. (Ed.). (2010). *Yeast*.

Nuclear Organisation

Academic publications

Tessadori, F., Zeng, K., Manders, E., Riool, M., Jackson, D. & Driel, R. van (2010). Stable S/MAR-based episomal vectors are regulated at the chromatin level. *Chromosome Research, 18*(7), 757-775.

Zanten, M. van, Tessadori, F., McLoughlin, F., Smith, R., Millenaar, F.F., Driel, R. van, Voesenek, L.A.C.J., Peeters, A.J.M. & Fransz, P. (2010). Photoreceptors CRYTOCHROME2 and phytochrome B control chromatin compaction in Arabidopsis. *Plant Physiology, 154*(4), 1686-1696.

Zanten, M. van, Tessadori, F., Bossen, L., Peeters, A.J.M. & Fransz, P. (2010). Large-scale chromatin de-compaction induced by low light is not accompanied by nucleosomal displacement. *Plant signaling and behavior, 5*(12), 1661-1662.

Luijsterburg, M.S., Bornstaedt, G. von, Gourdin, A.M., Politi, A.Z., Moné, M.J., Warmerdam, D.O., Goedhart, J., Vermeulen, W., Driel, R. van & Höfer, T. (2010). Stochastic and reversible assembly of a multiprotein DNA repair complex ensures accurate target site recognition and efficient repair. *Journal of Cell Biology, 189*(3), 445-463.

Haring, M., Bader, R., Louwers, M., Schwabe, A., Driel, R. van & Stam, M. (2010). The role of DNA methylation, nucleosome occupancy and histone modifications in paramutation. *Plant Journal, 63*(3), 366-378.

Scassellati, C., Albi, E., Cmarko, D., Tiberi, C., Cmarkova, J., Bouchet- Marquis, C., Verschure, P.J., Driel, R. van, Viola Magni, M. & Fakan, S. (2010). Intranuclear sphingomyelin is associated with transcriptionally active chromatin and plays a role in nuclear integrity. *Biology of the Cell, 102*(6), 361-375.

Book Chapters

Pavlova, P., Tessadori, F., Jong, H.J. de & Fransz, P. (2010). Immunocytological analysis of chromatin in isolated nuclei. In L. Hennig & C. Köhler (Eds.), *Plant developmental biology: methods and protocols* (Methods in molecular biology, 655) (pp. 413-432). New York: Humana Press.

Membership Editorial Board

Fransz, P.F. (Ed.). (2010). *Chromosome Research*.

Fransz, P.F. (Ed.). (2010). *Frontiers in Physiology*.

Prize

Verschure, P.J. (2010). Epigenetic gene regulation of the eukaryotic genome: Sytems Biology approaches using synthetic cell systems. Poster selected as 'the poster of the day'@The EMBO meeting: Barcelona, Spain (2010, September 04 - 2010, September 07). Erkenning.

Invited lectures

Fransz, P.F. (2010, December 14). *Global organization and dynamics of heterochromatin domains in Arabidopsis.* Köln, Germany, Max Planck Institute, seminar series (host: Dr. M. van Zanten).

Fransz, P.F. (2010, July 05). *A paracentric inversion in Arabidopsis thaliana.* Martonvasar, Hungary, seminar series (host: Dr. G. Linc).

Fransz, P.F. (2010, July 03). *Molecular and evolutionary aspects of a paracentric inversion in Arabidopsis thaliana.* Prague, Czech Republic, SEB Annual Main Meeting.

Stam, M.E. (2010, March 18). *b1 paramutation: the heritable transfer of epigenetic information in trans (selected from abstract).* Riva del Garde, Italy, Maize Meeting.

Stam, M.E. (2010, februari 10). *Gene regulation by distant regulatory elements.* Wageningen, the Netherlands, Keygene.

Verschure, P.J. (2010, October 04). *Epigenetic gene regulation of the eukaryotic genome: Sytems Biology approaches using synthetic cell systems.* Veldhoven, the Netherlands, Annual Dutch meeting on Molecular and Cellular Biophysics (FOM).

Verschure, P.J. (2010, June 03). *Epigenetic gene regulation of the eukaryotic genome: Sytems Biology approaches using synthetic cell systems.* Freiburg, Germany, SBMC 2010 Conference on Systems Biology of Mammalian cells.

Driel, R. van (2010, January 10). *Microfluidics and systems biology.* Leiden, the Netherlands, Lorentz Center Workshop on Microfuidics.

Driel, R. van (2010, November 10). *Understanding chromatin-associated processes in the living cell.* Hamburg, Germany, Heinrich Pette Instute.

Epigenetic Regulation of Gene Expression

Academic publications (refereed)

Hoeksema, F., Blokland, R., Siep, M., Hamer, C.M., Siersma, T., Blaauwen, J.L. den, Verhees, J.A. & Otte, A.P. (2010). The Use of a Stringent Selection System Allows the Identification of DNA Elements that Augment Gene Expression. *Molecular Biotechnology*.

Johanson, Z., Kearsley, A., Blaauwen, J. den, Newman, M. & Smith, M.M. (2010). No bones about it: An enigmatic Devonian fossil reveals a new skeletal framework—A potential role of loss of gene regulation. *Seminars in Cell & Developmental Biology, 21*(4), 414-423.

Inoue, K., Kohda, T., Sugimoto, M., Sado, T., Ogonuki, N., Matoba, S., Shiura, H., Ikeda, R., Mochida, K., Fujii, T., Sawai, K., Otte, A.P., Tian, X.C., Yang, X., Ishino, F., Abe, K. & Ogura, A. (2010). Impeding Xist expression from the active X chromosome improves mouse somatic cell nuclear transfer. *Science, 330*(6003), 496-499.

Molecular Cytology

Patent

Manders, E.M.M. (17-09-2010). Method and apparatus for shaping an image of an object. no JP2006-532114.

Academic publications

Subach, F.V., Zhang, L., Gadella, T.W.J., Gurskaya, N.G., Lukyanov, K.A. & Verkhusha, V.V. (2010). Red fluorescent protein with reversibly photoswitchable absorbance for photochromic FRET. *Chemistry & Biology, 17*(7), 745-755.

Tessadori, F., Zeng, K., Manders, E., Riool, M., Jackson, D. & Driel, R. van (2010). Stable S/MAR-based episomal vectors are regulated at the chromatin level. *Chromosome Research, 18*(7), 757-775.

Hoebe, R.A., Noorden, C.J.F. van & Manders, E.M.M. (2010). Noise effects and filtering in controlled light exposure microscopy. *Journal of Microscopy, 240*(3), 197-206.

Vos, W.H. de, Joss, G.H., Haffmans, W., Hoebe, R.A., Manders, E.M.M. & Van Oostveldt, P. (2010). Four-dimensional telomere analysis in recordings of living human cells acquired with Controlled Light Exposure. *Journal of Microscopy, 238*(3), 254-264.

Vos, W.H. de, Houben, F., Hoebe, R.A., Hennekam, R., Engelen, B. van, Manders, E.M.M., Ramaekers, F.C.S., Broers, J.L.V. & Oostveldt, P. van (2010). Increased plasticity of the nuclear envelope and hypermobility of telomeres due to the loss of A-type lamins. *Biochimica et Biophysica Acta G General Subjects, 1800*(4), 448-458.

Schultz, C., Neef, A.B., Gadella (jr.), T.W.J. & Goedhart, J. (2010). Imaging lipids in living cells. *Cold Spring Harbor protocols, 8*, pdb.top83.

Alexeeva, S., Gadella (jr.), T.W.J., Verheul, J., Verhoeven, G.S. & Blaauwen, T. den (2010). Direct interactions of early and late assembling division proteins in Escherichia coli cells resolved by FRET. *Molecular Microbiology, 77*(2), 384-398.

Goedhart, J., Weeren, L. van, Hink, M.A., Vischer, N.O.E., Jalink, K. & Gadella (jr.), T.W.J. (2010). Bright cyan fluorescent protein variants identified by fluorescence lifetime screening. *Nature Methods, 7*(2), 137-139.

Schultz, C., Neef, A.B., Gadella (jr.), T.W.J. & Goedhart, J. (2010). Labeling lipids for imaging in live cells. *Cold Spring Harbor protocols, 8*, pdb.prot5459.

Schultz, C., Neef, A.B., Gadella (jr.), T.W.J. & Goedhart, J. (2010). Labeling lipids for imaging fixed cells. *Cold Spring Harbor protocols, 8*, pdb.prot5458.

Schultz, C., Neef, A.B., Gadella (jr.), T.W.J. & Goedhart, J. (2010). Transfection of cells with DNA encoding a visible fluorescent protein-tagged lipid-binding domain. *Cold Spring Harbor protocols, 8*, pdb.prot5457.

Luijsterburg, M.S., Bornstaedt, G. von, Gourdin, A.M., Politi, A.Z., Moné, M.J., Warmerdam, D.O., Goedhart, J., Vermeulen, W., Driel, R. van & Höfer, T. (2010). Stochastic and reversible assembly of a multiprotein DNA repair complex ensures accurate target site recognition and efficient repair. *Journal of Cell Biology, 189*(3), 445-463.

Typas, A., Banzhaf, M., Berg van Saparoea, B. van den, Verheul, J., Biboy, J., Nichols, R.J., Zietek, M., Beilharz, K., Kannenberg, K., Rechenberg, M. von, Breukink, E., Blaauwen, T. den, Gross, C.A. & Vollmer, W. (2010). Regulation of peptidoglycan synthesis by outer-membrane proteins. *Cell, 143*(7), 1097-1109.

Schaffner-Barbero, C., Gil-Redondo, R., Ruiz-Avila, L.B., Huecas, S., Läppchen, T., Blaauwen, T. den, Diaz, J.F., Morreale, A. & Andreu, J.M. (2010). Insights into nucleotide recognition by cell division protein FtsZ from a mant-GTP competition assay and molecular dynamics. *Biochemistry, 49*(49), 10458-10472.

Soprova, Z., Sauri, A., Ulsen, P. van, Tame, J.R.H., Blaauwen, T. den, Jong, W.S.P. & Luirink, J. (2010). A conserved aromatic residue in the autochaperone domain of the autotransporter Hbp is critical for initiation of outer membrane translocation. *The Journal of Biological Chemistry, 285*(49), 38224-38233.

Potluri, L., Karczmarek, A., Verheul, J., Piette, A., Wilkin, J.M., Werth, N., Banzhaf, M., Vollmer, W., Young, K.D., Nguyen-Distèche, M. & Blaauwen, T. den (2010). Septal and lateral wall localization of PBP5, the major D,D-carboxypeptidase of Escherichia coli, requires substrate recognition and membrane attachment. *Molecular Microbiology, 77*(2), 300-323.

Oomen, C.A., Soeters, H., Audureau, N., Vermunt, L., Hasselt, F.N. van, Manders, E.M.M., Joëls, M., Lucassen, P.J. & Krugers, H. (2010). Severe early life stress hampers spatial learning and neurogenesis, but improves hippocampal synaptic plasticity and emotional learning under high-stress

conditions in adulthood. *Journal of Neuroscience, 30*(19), 6635-6645.

Membership editorial board

Blaauwen, T. den (Ed.). (2010). *Microbiology*.

Invited lectures

Ploeg, R. van der & Blaauwen, T. den (2010, October 02). *Protein interaction, localization and function; unraveling the assembly of the Divisome complex.* Baeza, Spain, Workshop "The Dynamics of Peptidoglycan Structure and Function: New Insights into the 'Great Wall".

Blaauwen, T. den (2010, November 22). *Morphogenesis of E. coli.* Kaiserslautern, Germany, seminar.

Blaauwen, T. den (2010, April 28). *Spatiotemporal organization of the rod shaped bacterium cell wall elongation and division.* Delft, the Netherlands, TU Delft.

Blaauwen, T. den (2010, March 29). *Septal and lateral wall localization of the major D,D-carboxypeptidase PBP5 of Escherichia coli requires substrate recognition and membrane attachment rather than protein interactions.* Orsay, France, seminar.

Ploeg, R. van der & Blaauwen, T. den (2010, March 16). *In vivo and in vitro FRET in bacteria.* Cambridge, U.K., Divinocell.

Goedhart, J. (2010, October 05). *Visualizing signal transduction using genetically encoded fluorescent probes.* Stockholm, Sweden, Karolinska Institutet te Stockholm.

Blaauwen, T. den (2010, December 08). *Morphogenesis of E. coli.* Newcastle, U.K., University of NewCastle, Institute for Bacterial Cell biology.

Blaauwen, T. den (2010, December 08). *Morphogenesis of E. coli.* Coventry, U.K., University of Warwick, Institute for Bacterial Cell biology.

Blaauwen, T. den (2010, September 30). *EDT: Structure and Function of Biological Macromolecules, Modelling and Bioinformatics). Divinocell network Exploiting Gram-negative cell division targets in the test tube to obtain antimicrobial compounds.* Harzé, Belgium, European Inter-network Meeting Aeropath, AntiPathoGN, Divinocell, EUR-INTAFAR, Nabativi, PAR, Pneumopath, UK Bacwan. Organized by the Centre of Protein Engineering and the Doctoral School of Sciences.

Gadella, T.W.J. (2010, February 23). *New probes for FRET imaging.* Basel, Switserland, Inst. Biochemistry and Genetics, Dept. for Biomedicine, University of Basel.

Gadella, T.W.J. (2010, March 19). *Enlightening cellular signalling dynamics with genetic encoded sensors and microscopy.* Leiden, Institute of Biology, Leiden University.

Gadella, T.W.J. (2010, April 15). *FRET-microscopy.* Rotterdam. OIC advanced course. Erasmus Medical Centre.

Gadella, T.W.J. (2010, May 4). *New probe-based strategies for quantitative microscopy of signaling dynamics in single cells.* Ashburn, VA, USA. Novel approaches to Bioimaging II international symposium. Howard Hughes Medical Institute Janelia Farm.

Gadella, T.W.J. (2010, May 28). *New probe-based strategies for quantitative microscopy of signaling dynamics in single cells.* Warsaw, Poland. ESMI, 5th European Molecular Imaging Meeting EMIM2010.

Gadella, T.W.J. (2010, June 3). *New probe strategies for quantitative imaging of subcellular signalling dynamics.* Amsterdam. SILS research day, University of Amsterdam.

Gadella, T.W.J. (2010, June 8). *Quantitative imaging of molecular interactions and conformation in living cells.* Amsterdam. NBIC-SIB summer school on 'Quantitative imaging and modelling of biological problems.'

Gadella, T.W.J. (2010, June 17). *New probes for quantitative imaging of subcellular signalling dynamics.* Toulouse, France. 6th European Nodperception meeting.

Gadella, T.W.J. (2010, June 29). *Optimizing fluorescent proteins for FRET applications by FLIM screening.* Londen, UK. Microscience 2010 conference.

Gadella, T.W.J. (2010, September 20), *FRET-microscopy*. Wageningen, FEBS advanced course on Microspectroscopy: Probing Protein Dynamics and Interactions in Living Cells, University of Wageningen.

Gadella, T.W.J. (2010, September 22), *The green revolution: seeing is believing.* Amsterdam. Lecture Genootschap ter bevordering van Natuur-Genees- en Heelkunde, Sanquin, Amsterdam.

Gadella, T.W.J. (2010, October 26), *FRET-microscopy*. Rotterdam. OIC advanced course. Erasmus Medical Centre.

Gadella, T.W.J. (2010, November 23). *The microscopy and bioimaging revolution: seeing is believing.* Utrecht, NGI Life Sciences Momentum.

Gadella, T.W.J. (2010, December 9). *Multimode FLIM and FRET.* Groningen. B-Basic Masterclass Single Molecule and Single Cell Analysis. University of Groningen.

Gadella, T.W.J. (2010, December 17). *Quantitative imaging of signal transduction across the membrane*, Amsterdam. AIMMS-VU/NISB workshop, Free University of Amsterdam.

Goedhart, J. (2010, October 5). *Visualizing signal transduction using genetically encoded fluorescent probes.* Stockholm, Sweden. Live-Cell-Imaging Course, Karolinska Institutet, Stockholm.

Hink, M.A. (2010, February 17). *Introduction to Fluorescence Correlation Spectroscopy.* Berlin, Germany, 2nd European Short Course on Time-Resolved Microscopy and Correlation Spectroscopy.

Hink, M.A. (2010, April 10). *Super-resolution Microscopy.* Rotterdam, the Netherlands, 8th IEEE International Symposium on Biomedical Imaging (ISBI 2010).

Hink, M.A. (2010, May 28). *Super-resolution Microscopy.* Amsterdam, the Netherlands, Confocal Microscopy course: Fundamentals, Advanced techniques and Biological Applications.

Hink, M.A. (2010, September 20). *Fluorescence fluctuation spectroscopy.* Wageningen, the Netherlands, FEBS advanced course Microspectroscopy: Probing Protein Dynamics and Interactions in Living Cells.

Manders, E.M.M. (2010, September 24). *Controlled Light Exposure Microscopy in Neurobiology.* Ghent, Belgium, Advanced Microscopy Symposium 2010.

Manders, E.M.M. (2010, March 24). *Controlled Light Exposure Microscopy; practical implementation.* Yokohama, Japan, Nikon Head Quarters.

Manders, E.M.M. (2010, March 28). *Quantitative measurement of colocalization in confocal microscopy.* Shanghai, China, Focus on Microscopy 2010.

Kedziora, K., Hagenston, A., Kuzak, M.T., Zhou, M., Zoon, P.D., Lambrechts, S.A.G., Goedhart, J., Krugers, H., Bading, H., Dobrucki, J.W. & Manders, E.M.M. (2010, March 30). *Calcium imaging with strongly reduced phototoxicity and photobleaching by Wide-Field Controlled Light Exposure Microscopy (WF-CLEM).* Shanghai, China, Focus on Microscopy 2010.

Manders, E.M.M., Hink, M.A. & Voort, H.T.M. van der (2010, April 14). *Optical microscopy, deconvolution and Super resolution.* Rotterdam, the Netherlands, 2010 IEEE, International Symposium on Biomedical Imaging: From Nano to Macro.

Postma, M. (2010, October 28). *Robustness, sensitivity and dynamical behavior of a Drosophila gap gene pattern formation model.* Barcelona, Spain, Reverse-engineering development meeting, CRG.

Appendix 2

Research Programme **Plant Signalling**

Plant Physiology

PhD Thesis

Arisz, S.A. (2010, September 08). *Plant Phosphatidic Acid Metabolism in Response to Environmental Stress.* UvA Universiteit van Amsterdam (166 pag.). Prom./coprom.: prof.dr. M.A. Haring & dr. T. Munnik.

Academic publications

Allmann, S. & Baldwin, I.T. (2010). Insects betray themselves in nature to predators by rapid isomerization of green leaf volatiles. *Science, 329*(5995), 1075-1078.

Zanten, M. van, Tessadori, F., McLoughlin, F., Smith, R., Millenaar, F.F., Driel, R. van, Voesenek, L.A.C.J., Peeters, A.J.M. & Fransz, P. (2010). Photoreceptors CRYTOCHROME2 and phytochrome B control chromatin compaction in Arabidopsis. *Plant Physiology, 154*(4), 1686-1696.

Park, D.H., Mirabella, R., Bronstein, P.A., Preston, G.M., Haring, M.A., Lim, C.K., Collmer, A. & Schuurink, R.C. (2010). Mutations in γ-aminobutyric acid (GABA) transaminase genes in plants or Pseudomonas syringae reduce bacterial virulence. *Plant Journal, 64*(2), 318-330.

Burg, H.A. van den, Kini, R.K., Schuurink, R.C. & Takken, F.L.W. (2010). Arabidopsis small ubiquitin-like modifier paralogs have distinct functions in development and defense. *The Plant Cell, 22*(6), 1998-2016.

Ament, K., Krasikov, V., Allmann, S., Rep, M., Takken, F.L.W. & Schuurink, R.C. (2010). Methyl salicylate production in tomato affects biotic interactions. *Plant Journal, 62*(1), 124-134.

Munnik, T. & Vermeer, J.E.M. (2010). Osmotic stress-induced phosphoinositide and inositol phosphate signalling in plants. *PLANT CELL ENVIRON, 33*(4), 655-669.

Vossen, J.H., Abd-El-Haliem, A., Fradin, E.F., Berg, G.C.M. van den, Ekengren, S.K., Mayjer, H.J.G., Seifi, A., Bai, Y., Have, A. ten, Munnik, T., Thomma, B.P.H.J. & Joosten, M.H.A.J. (2010). Identification of tomato phosphatidylinositol-specific phospholipase-C (PI-PLC) family members and the role of PLC4 and PLC6 in HR and disease resistance. *Plant Journal, 62*(2), 224-239.

Monreal, J.A., McLoughlin, F., Echevarría, C., García-Mauriño, S. & Testerink, C. (2010). Phosphoenolpyruvate carboxylase from C4 leaves is selectively targeted for inhibition by anionic phospholipids. *Plant Physiology, 152*(2), 634-638.

Dhonukshe, P., Huang, F., Galvan-Ampudia, C.S., Mähönen, A.P., Kleine-Vehn, J., Xu, J., Quint, A., Prasad, K., Friml, J., Scheres, B. & Offringa, R. (2010). Plasma membrane-bound AGC3 kinases phosphorylate PIN auxin carriers at TPRXS(N/S) motifs to direct apical PIN recycling. *DEVELOPMENT, 137*(19), 3245-3255.

Huang, F., Kemel Zago, M., Abas, L., Marion, A. van, Galván-Ampudia, C.S. & Offringa, R. (2010). Phosphorylation of conserved PIN motifs directs Arabidopsis PIN1 polarity and auxin transport. *The Plant Cell, 22*(4), 1129-1142.

Allmann, S., Halitschke, R., Schuurink, R.C. & Baldwin, I.T. (2010). Oxylipin channelling in Nicotiana attenuata: lipoxygenase 2 supplies substrates for green leaf volatile production. *PLANT CELL ENVIRON, 33*(12), 2028-2040.

Book Chapters

Lee, Y., Munnik, T. & Lee, Y. (2010). Plant phosphatidylinositol 3-kinase. In T. Munnik (Ed.), *Lipid signaling in plants* (Plant cell monographs, 16) (pp. 95-106). Heidelberg: Spinger.

Arisz, S.A. & Munnik, T. (2010). Diacylglycerol kinase. In T. Munnik (Ed.), *Lipid signaling in plants* (Plant cell monographs, 16) (pp. 107-114). Heidelberg: Springer.

Vermeer, J.E.M. & Munnik, T. (2010). Imaging lipids in living plants. In T. Munnik (Ed.), *Lipid signaling in plants* (Plant cell monographs, 16) (pp. 185-199). Heidelberg: Springer.

Kooijman, E.E. & Testerink, C. (2010). Phosphatidic acid: an electrostatic/hydrogen-bond switch? In T. Munnik (Ed.), *Lipid signaling in plants* (Plant cell monographs, 16) (pp. 203-222). Heidelberg: Springer.

Book editing

Munnik, T. (Ed.). (2010). *Lipid signaling in plants* (Plant cell monographs, 16). Heidelberg: Spinger.

Membership editorial board

Munnik, T. (Ed.). (2010). *Frontiers in Physiology*.

Munnik, T. (Ed.). (2010). *Plant signaling and behavior*.

Munnik, T. (Ed.). (2010). *The Open Plant Science Journal*.

Invited lectures

Galvan Ampudia, C.S. (2010, September 06). *Novel salt stress-induced signals that control the direction of plant root growth.* Durham, United Kingdom., Genomic Arabidopsis Resource Network (GARNet) Meeting.

Testerink, C. (2010, September 19). *Salt stress-induced lipid signals and protein kinase pathways controlling root growth.* Adelaide, Australia, International Workshop on Plant Membrane Biology.

Galvan Ampudia, C.S. (2010, November 04). *Novel salt stress-induced lipid signals and protein kinase pathways controlling root growth.* Amsterdam, the Netherlands, 2nd EPS Cell Signaling Symposium.

Munnik, T. (2010, September 19). *Membrane trafficking, lipid metabolism and lipid-transporter interactions (Plenary presentation).* Adelaide, Australia, 15th International Workshop on Plant Membrane Biology.

Munnik, T. (2010, July 11). *Phospholipid Metabolism in Plant Stress and Development.* Cairns, Australia, International Symposium on Plant Lipids (ISPL 2010.

Munnik, T. (2010, November 22). *Learning the lipid language of plant signalling.* Cuernavaca, Mexico, Frontiers in Genomics - Seminar I; National University of México (UNAM).

Munnik, T. (2010, November 23). *Phospholipid signalling in plant stress and development.* Cuernavaca, Mexico, Frontiers in Genomics - Seminar II; Center for Genomic Sciences (CCG), Institute of Biotechnology (IBT).

Testerink, C. (2010, June 13). *Novel salt stress-induced signals that control the direction of plant root growth.* Les Diablerets, Switzerland, Gordon Research Conference on Salt and Water Stress in Plants.

Testerink, C. (2010, May 22). *SnRK2 protein kinases directly bind the lipid second messenger phosphatidic acid and are involved in the response of Arabidopsis roots to salinity.* Valencia, Spain, The Third meeting of FA0605 "Plant Abiotic Stress: from signalling to crop improvement".

Schuurink, R.C. (2010, November 24). *Reactive electrophile species.* Amsterdam, the Netherlands, EPS signaling symposium.

Munnik, T. (2010, April 22). *Phospholipid Metabolism in Plant Stress and Development.* Valencia, Spain, Plant Abiotic Stress; from Signalling to Crop Improvement.

Haring, M.A. (2010, November 18). *Plant Insect Interactions.* Haren / Groningen, the Netherlands, seminar.

Munnik, T. (2010, July 02). *Polyphosphoinositides in membrane trafficking during plant stress and development.* Amsterdam, the Netherlands, EPS workshop - 'Endomembranes in plants'.

Munnik, T. (2010, June 13). *Signaling pathways in osmotic stress.* Les Diablerets, Switzerland, Gordon Research Conference (GRC) on Salt & Water Stress in Plants.

Haring, M.A. (2010, November 12). *Modern Plant Breeding techniques.* Bad Vilbel, Germany, workshop.

Haring, M.A. (2010, January 29). *Modern Plant Breeding techniques.* Witzenhausen, Germany, University of Kasse: workshop.

Haring, M.A. (2010). *Plant communication.* Witzenhausen, Germany, University of Kassel.

Molecular Plant Pathology

Academic publications

Burg, H.A. van den & Takken, F.L.W. (2010). SUMO-, MAPK-, and resistance protein-signaling converge at transcription complexes that regulate plant innate immunity. *Plant signaling and behavior, 5*(12), 1587-1591.

Ooijen, G. van, Lukasik, E., Burg, H.A. van den, Vossen, J.H., Cornelissen, B.J.C. & Takken, F.L.W. (2010). The small heat shock protein 20 RSI2 interacts with and is required for stability and function of tomato resistance protein I-2. *Plant Journal, 63*(4), 563-572.

Rep, M. & Kistler, H.C. (2010). The genomic organization of plant pathogenicity in Fusarium

species. *Current Opinion in Plant Biology, 13*(4), 420-426.

Takken, F. & Rep, M. (2010). The arms race between tomato and Fusarium oxysporum. *Molecular Plant Pathology, 11*(2), 309-314.

Ma, L.J., Does, H.C. van der, Borkovich, K.A., Coleman, J.J., Daboussi, M.J., Di Pietro, A., Dufresne, M., Freitag, M., Grabherr, M., Henrissat, B., Houterman, P.M., Kang, S., Shim, W.B., Woloshuk, C., Xie, X., Xu, J.-R, Antoniw, J., Baker, S.E., Bluhm, B.H., Breakspear, A., Brown, D.W., Butchko, R.A.E., Chapman, S., Coulson, R., Coutinho, P.M., Danchin, E.G.J., Diener, A., Gale, L.R., Gardiner, D.M., Goff, S., Hammond-Kosack, K.E., Hilburn, K., Hua-Van, A., Jonkers, W., Kazan, K., Kodira, C.D., Koehrsen, M., Kumar, L., Lee, Y.H., Li, L., Manners, J.M., Miranda-Saavedra, D., Mukherjee, M., Park, G., Park, J., Park, S.Y., Proctor, R.H., Regev, A., Ruiz-Roldan, M.C., Sain, D., Sakthikumar, S., Sykes, S., Schwartz, D.C., Gillian Turgeon, B., Wapinski, I., Yoder, O., Young, S., Zeng, Q., Zhou, S., Galagan, J., Cuomo, C.A., Kistler, H.C. & Rep, M. (2010). Comparative genomics reveals mobile pathogenicity chromosomes in Fusarium. *Nature, 464*(7287), 367-373.

Burg, H.A. van den, Kini, R.K., Schuurink, R.C. & Takken, F.L.W. (2010). Arabidopsis small ubiquitin-like modifier paralogs have distinct functions in development and defense. *The Plant Cell, 22*(6), 1998-2016.

Ament, K., Krasikov, V., Allmann, S., Rep, M., Takken, F.L.W. & Schuurink, R.C. (2010). Methyl salicylate production in tomato affects biotic interactions. *Plant Journal, 62*(1), 124-134.

Invited lectures

Rep, M. (2010, November 18). *Genomic organization of virulence in the fungus Fusarium oxysporum.* Leiden, the Netherlands, IBL Symposium “The new Biology: the Impact of Genomics on Biology".

Rep, M. (2010, July 04). *The tomato / Fusarium oxysporum pathosystem.* Valencia, Spain, XVII Congress of the Federation of European Societies of Plant Biology (FESPB).

Rep, M. (2010, June 16). *Pathogenicity chromosomes of Fusarium oxysporum (Keynote lecture).* Wageningen, the Netherlands, Spring meeting of the Royal Dutch Phytopathological Society (KNPV).

Rep, M. (2010, June 06). *The molecular basis of pathogenicity in fungi (Keynote lecture).* Toulouse, France, Oomycete Molecular Genetics Network Meeting.

Rep, M. (2010, March 29). *Effectors of Fusarium oxysporum.* Noordwijkerhout, the Netherlands, 10th European Conference on Fungal Genetics.

Rep, M. (2010, March 22). *Genome dynamics and host-specific virulence in plant pathogenic fungi.* University of Turin, Italy, Mycological Snapshots, workshop organised by the PhD School of Science and High Technology, Course Biology and Biotechnology of Fungi, Plant Biology Department.

Takken, F.L.W. (2010, June 08). *Functional analysis of Fusarium oxysporum f.sp. lycopersici effector proteins.* Freising, Germany, DFG funded colloquium: 'Microbial reprogramming of plant cell development' priority project SPP1212 'Plant-Micro'.

Takken, F.L.W. (2010, October 08). *Molecular co-evolution in the tomato-Fusarium pathosystem.* Giessen, Germany, Justus Liebig University , Giessen, Germany.

Takken, F.L.W. (2010, May 11). *The arms race between effectors of Fusarium oxysporum and resistance proteins of tomato.* Durham, UK, Seminar series School of Biological and Biomedical Sciences, Durham University.

Appendix 3

Research Programme **SILS Center for NeuroScience**

Cognitive and Systems Neuroscience

PhD Thesis

Lee, E. (2010, April 14). *Neural coding of attention and attentional set shifting in the rat medial prefrontal cortex.* UvA Universiteit van Amsterdam (140 pag.). Prom./coprom.: prof.dr. C.M.A. Pennartz.

Huijbers, W. (2010, December 17). *Episodic memory and the role of the brain's default-mode network.* UvA Universiteit van Amsterdam (139 pag.). Prom./coprom.: prof.dr. C.M.A. Pennartz & dr. S.M. Daselaar.

Academic publications (refereed)

Daselaar, S.M., Porat, Y., Huijbers, W. & Pennartz, C.M.A. (2010). Modality-specific and modality-independent components of the human imagery system. *NeuroImage, 52*(2), 677-685.

Kalenscher, T., Lansink, C.S., Lankelma, J.V. & Pennartz, C.M.A. (2010). Reward-associated gamma oscillations in ventral striatum are regionally differentiated and modulate local firing activity. *Journal of Neurophysiology, 103(3)*, 1658-1672.

Wingerden, M. van, Vinck, M., Lankelma, J.V. & Pennartz, C.M.A. (2010). Learning-associated gamma-band phase-locking of action–outcome selective neurons in orbitofrontal cortex. *Journal of Neuroscience, 30*(30), 10025-10038.

Kalenscher, T., Tobler, P.N., Huijbers, W., Daselaar, S.M. & Pennartz, C.M.A. (2010). Neural signatures of intransitive preferences. *Frontiers in Human Neuroscience, 4*, 49.

Meer, M.A.A. van der, Kalenscher, T., Lansink, C.S., Pennartz, C.M.A., Berke, J.D. & Redish, A.D. (2010). Integrating early results on ventral striatal gamma oscillations in the rat. *Frontiers in neuroscience, 4*, 300.

Sanchez-Fibla, M., Bernardet, U., Wasserman, E., Pelc, T., Mintz, M., Jackson, J.C., Lansink, C., Pennartz, C. & Verschure, P.F.M.J. (2010). Allostatic control for robot behavior regulation: a comparative rodent-robot study. *Advances in complex systems, 13*(3), 377-403.

Vinck, M.A., Oostenveld, R., Wingerden, E.J.M. van, Battaglia, F.P. & Pennartz, C.M.A. (2010). An improved index of phase-synchronization for electrophysiological data in the presence of volume-conduction, noise and sample-size bias. *NeuroImage*.

Lansink, C.S., Goltstein, P.M., Lankelma, J.V. & Pennartz, C.M.A. (2010). Fast-spiking interneurons of the rat ventral striatum: temporal coordination of activity with principal cells and responsiveness to reward. *European Journal of Neuroscience, 32*(3), 494-508.

Peyrache, A., Benchenane, K., Khamassi, M., Wiener, S.I. & Battaglia, F.P. (2010). Principal component analysis of ensemble recordings reveals cell assemblies at high temporal resolution. *Journal of computational neuroscience, 29*(1-2), 309-325.

Wingerden, M. van, Vinck, M., Lankelma, J. & Pennartz, C.M.A. (2010). Theta-band phase locking of orbitofrontal neurons during reward expectancy. *Journal of Neuroscience, 30*(20), 7078-7087.

Peyrache, A., Benchenane, K., Khamassi, M., Wiener, S.I. & Battaglia, F.P. (2010). Sequential reinstatement of neocortical activity during slow oscillations depends on cells' global activity. *Frontiers in systems neuroscience, 3*, 18.

Malkki, H.A.I., Donga, L.A.B., Groot, S.E. de, Battaglia, F.P., Brussaard, A.B., Borst, J.G.G., Elgersma, Y., Galjart, N., Horst, G.T. van der, Levelt, C.N., Pennartz, C.M.A., Smit, A.B., Spruijt, B.M., Verhage, M. & Zeeuw, C.I. de (2010). Appetitive operant conditioning in mice: heritability and dissociability of training stages. *Frontiers in behavioral neuroscience, 4*, 171.

Benchenane, K., Peyrache, A., Khamassi, M., Tierney, P.L., Gioanni, Y., Battaglia, F.P. & Wiener, S.I. (2010). Coherent theta oscillations and reorganization of spike timing in the hippocampal-prefrontal network upon learning. *Neuron, 66*(6), 921-936.

Huijbers, W., Pennartz, C.M.A. & Daselaar, S.M. (2010). Dissociating the "retrieval success"

regions of the brain: Effects of retrieval delay. *Neuropsychologia, 48*(2), 491-497.

Vinck, M., Wingerden, M. van, Womelsdorf, T., Fries, P. & Pennartz, C.M.A. (2010). The pairwise phase consistency: A bias-free measure of rhythmic neuronal synchronization. *NeuroImage, 51*(1), 112-122.

Kalenscher, T., Lansink, C.S., Lankelma, J.V. & Pennartz, C.M.A. (2010). Reward-associated gamma oscillations in ventral striatum are regionally differentiated and modulate local firing activity. *Journal of Neurophysiology, 103*(3), 1658-1672.

Daselaar, S.M., Huijbers, W., Jonge, M. de, Goltstein, P.M. & Pennartz, C.M.A. (2010). Experience-dependent alterations in conscious resting state activity following perceptuomotor learning. *Neurobiology of Learning and Memory, 93*(3), 422-427.

Kim, H., Daselaar, S.M. & Cabeza, R. (2010). Overlapping brain activity between episodic memory encoding and retrieval: Roles of the task-positive and task-negative networks. *NeuroImage, 49*(1), 1045-1054.

Book chapters

Kalenscher, T. & Pennartz, C.M.A. (2010). Do intransitive choices reflect genuinely context-dependent preferences? In M Delgado, E.A. Phelps & T.W. Robbins (Eds.), *Decision Making, Affect, and Learning* (pp. 235-256). Oxford University Press..

Lopes da Silva, F.H. (2010). EEG: Origin and Measurement. In C. Mulert & L. Lemieux (Eds.), *EEG-fMRI: Physiological Basis, Technique, and Applications* (pp. 19-38). Berlin, Germany: Springer Verlag.

Lopes da Silva, F.H. (2010). EEG: Origin and Measurement. In C. Mulert & L. Lemieux (Eds.), *EEG-fMRI: Physiological Basis, Technique, and Applications* (pp. 19-38). Berlin, Germany: Springer Verlag.

Kalenscher, T. (2010). Decision-making and neuroeconomics. In *Encyclopedia of life sciences*. New York: Wiley.

Membership editorial board

Kalenscher, T. (Ed.). (2010). *Journal of Neuroscience*.

Kalenscher, T. (Ed.). (2010). *Journal of Neurophysiology*.

Kalenscher, T. (Ed.). (2010). *NeuroImage*.

Kalenscher, T. (Ed.). (2010). *European Journal of Neuroscience*.

Kalenscher, T. (Ed.). (2010). *Cortex*.

Kalenscher, T. (Ed.). (2010). *Behavioural Brain Research*.

Kalenscher, T. (Ed.). (2010). *Current Biology*.

Kalenscher, T. (Ed.). (2010). *Neuroscience*.

Kalenscher, T. (Ed.). (2010). *BEHAV NEUROSCI*.

Kalenscher, T. (Ed.). (2010). *Physiology and Behaviour*.

Kalenscher, T. (Ed.). (2010). *Social Neuroscience*.

Kalenscher, T. (Ed.). (2010). *Neurotoxicity Research*.

Kalenscher, T. (Ed.). (2010). *Cognitive Affective & Behavioral Neuroscience*.

Invited lectures

Kalenscher, T. (2010, January 22). *Decisions, Utility Functions and the Brain.* Hamburg Germany, lecture at symposium.

Kalenscher, T. (2010, February 27). *Our Brother's Keeper? Understanding Attitudes Toward Health Care Systems From A Decision Making Perspective.* Nairobi, Kenya, Invited talk.

Kalenscher, T. (2010, May 22). *Neural Signatures of Intransitive Preferences.* Qingdao, China, Invited talk at conference.

Kalenscher, T. (2010, June 07). *Neuroeconomics – An Exciting Joint Venture.* Amsterdam, The Netherlands, Invited talk at Summer School.

Kalenscher, T. (2010, October 28). *Economic Value and its Representation in the Brain.* Zurich, Switzerland, talk at Symposium.

Kalenscher, T. (2010, November 09). *Economic Value and its Representation in the Brain.* Bonn, Germany, talk at Symposium.

Kalenscher, T. (2010, December 03). *The Düsseldorf Decision Making Group.* Bonn, Germany, Talk at Symposium.

Pennartz, C.M.A. (2010, January 20). *Neural mechanisms for reward prediction and memory formation in prefrontal cortex, hippocampus and striatum.* Pécs Hungary, International workshop of the International Brain Research Organization.

Pennartz, C.M.A. (2010, January 27). *Memory, emotion and sleep.* Amsterdam, The Netherlands, Lecture for Studium Generale, CREA.

Pennartz, C.M.A. (2010, December 14). *Interweaving neural substrates for memory,*

motivation and perception. Osnabrück, Germany, Seminar at University of Osnabrück.

Pennartz, C.M.A. (2010, March 16). *Memory reactivation during sleep and rest:ensemble recordings and fMRI studies.* Oxford, Seminar at University of Oxford.

Cellular and Systems Neurobiology

PhD Thesis

Çağnan, H. (2010, December 07). *Basic mechanisms of DBS for Parkinson's disease: computational and experimental studies on neural dynamics.* UvA Universiteit van Amsterdam (228 pag.). Prom./coprom.: prof.dr. W.J. Wadman & H.C.F. Martens.

Smit-Rigter, L.A. (2010, December 15). *The role of the serotonin 5-Ht3 receptor in cortical development.* UvA Universiteit van Amsterdam (177 pag.) (Amsterdam). Prom./coprom.: prof.dr. W.J. Wadman & dr. J.A. van Hooft.

Academic publications

Smit-Rigter, L.A., Wadman, W.J. & Hooft, J.A. van (2010). Impaired social behavior in 5-HT(3A) receptor knockout mice. *Frontiers in behavioral neuroscience, 4*, 169.

Vliet, E.A. van, Edelbroek, P.M. & Gorter, J.A. (2010). Improved seizure control by alternating therapy of levetiracetam and valproate in epileptic rats. *Epilepsia, 51*(3), 362-370.

Vliet, E.A. van, Zibell, G., Pekcec, A., Schlichtiger, J., Edelbroek, P.M., Holtman, L., Aronica, E., Gorter, J.A. & Potschka, H. (2010). COX-2 inhibition controls P-glycoprotein expression and promotes brain delivery of phenytoin in chronic epileptic rats. *NEUROPHARMACOLOGY, 58*(2), 404-412.

Iyer, A.M., Zurolo, E., Boer, K., Baayen, J.C., Giangaspero, F., Arcella, A., Di Gennaro, G.C., Esposito, V., Spliet, W.G.M., Rijen, P.C. van, Troost, D., Gorter, J.A. & Aronica, E. (2010). Tissue plasminogen activator and urokinase plasminogen activator in human epileptogenic pathologies. *Neuroscience, 167*(3), 929-945.

Aronica, E., Fluiter, K., Iyer, A., Zurolo, E., Vreijling, J., Vliet, E.A. van, Baayen, J.C. & Gorter, J.A. (2010). Expression pattern of miR-146a, an inflammation-associated microRNA, in experimental and human temporal lobe epilepsy. *European Journal of Neuroscience, 31*(6), 1100-1107.

Wyckhuys, T., Staelens, S., Van Nieuwenhuyse, B., Deleye, S., Hallez, H., Vonck, K., Raedt, R., Wadman, W. & Boon, P. (2010). Hippocampal deep brain stimulation induces decreased rCBF in the hippocampal formation of the rat. *NeuroImage, 52*(1), 55-61.

Noam, Y., Zha, Q., Phan, L., Wu, R.L., Chetkovich, D.M., Wadman, W.J. & Baram, T.Z. (2010). Trafficking and surface expression of hyperpolarization-activated cyclic nucleotide-gated channels in hippocampal neurons. *The Journal of Biological Chemistry, 285*(19), 14724-14736.

Wyckhuys, T., Raedt, R., Vonck, K., Wadman, W.J. & Boon, P. (2010). Comparison of hippocampal Deep Brain Stimulation with high (130 Hz) and low frequency (5 Hz) on afterdischarges in kindled rats. *Epilepsy Research, 88*(2-3), 239-246.

Carette, E., Vonck, K., De Herdt, V., Van Dycke, A., El Tahry, R., Meurs, A., Raedt, R., Goossens, L., Van Zanddijcke, M., Van Maele, G., Thadani, V., Wadman, W., Van Roost, D. & Boon, P. (2010). Predictive factors for outcome of invasive video-EEG monitoring and subsequent resective surgery in patients with refractory epilepsy. *Clinical Neurology and Neurosurgery, 112*(2), 118-126.

Holtman, L., Vliet, E.A. van, Edelbroek, P.M., Aronica, E. & Gorter, J.A. (2010). Cox-2 inhibition can lead to adverse effects in a rat model for temporal lobe epilepsy. *Epilepsy Research, 91*(1), 49-56.

Gorter, J.A., Zurolo, E., Lyer, A., Fluiter, K., Vliet, E.A. van, Baayen, J.C. & Aronica, E. (2010). Induction of sodium channel Nax (SCN7A) expression in rat and human hippocampus in temporal lobe epilepsy. *Epilepsia, 51*(9), 1791-1800.

Gorter, J.A. (2010). Microarray-studies bij epileptische ratten indiceren nieuwe therapeutische strategieën. *Epilepsie, 8*(4), 12-15.

Lyer, A., Zurolo, E., Spliet, W.G.M., Rijen, P.C. van, Baayen, J.C., Gorter, J.A. & Aronica, E. (2010). Evaluation of the innate and adaptive immunity in type I and type II focal cortical dysplasias. *Epilepsia, 51*(9), 1763-1773.

Zurolo, E., Iyer, A.M., Spliet, W.G.M., Rijen, P.C. van, Troost, D., Gorter, J.A. & Aronica, E. (2010). CB1 and CB2 cannabinoid receptor expression during development and in epileptogenic developmental pathologies. *Neuroscience, 170*(1), 28-41.

Noam, Y. & Baram, T.Z. (2010). Hyperpolarized views on the roles of the

hyperpolarization-activated channels in neuronal excitability. *Epilepsy currents, 10*(1), 28-30.

Vucurovic, K., Gallopin, T., Ferezou, I., Rancillac, A., Chameau, P., Hooft, J.A. van, Geoffroy, H., Monyer, H., Rossier, J. & Vitalis, T. (2010). Serotonin 3A receptor subtype as an early and protracted marker of cortical interneuron subpopulations. *Cerebral Cortex, 20*(10), 2333-2347.

De Herdt, V., De Waele, J., Raedt, R., Wyckhuys, T., El Tahry, R., Vonck, K., Wadman, W. & Boon, P. (2010). Modulation of seizure threshold by vagus nerve stimulation in an animal model for motor seizures. *ACTA NEUROL SCAND, 121*(4), 271-276.

Schenk, G.J., Werkman, T., Wadman, W., Veldhuisen, B., Dijkmans, T.F., Blaas, E., Kegel, L., Kloet, E.R. de & Vreugdenhil, E. (2010). Over-expression of the DCLK gene transcript CARP decreases CA3/CA1 network excitability. *Brain Research, 1352*, 21-34.

Van Dycke, A., Raedt, R., Verstraete, A., Theofilas, P., Wadman, W., Vonck, K., Boison, D. & Boon, P. (2010). Astrocytes derived from fetal neural progenitor cells as a novel source for therapeutic adenosine delivery. *Seizure, 19*(7), 390-396.

Wyckhuys, T., Boon, P., Raedt, R., Van Nieuwenhuyse, B., Vonck, K. & Wadman, W. (2010). Suppression of hippocampal epileptic seizures in the kainate rat by Poisson distributed stimulation. *Epilepsia, 51*(11), 2297-2304.

El Tahry, R., Raedt, R., Mollet, L., De Herdt, V., Wyckuys, T., Van Dycke, A., Meurs, A., Dewaele, F., Van Roost, D., Doguet, P., Delbeke, J., Wadman, W., Vonck, K. & Boon, P. (2010). A novel implantable vagus nerve stimulation system (ADNS-300) for combined stimulation and recording of the vagus nerve: Pilot trial at Ghent University Hospital. *Epilepsy Research, 92*(2-3), 231-239.

Boer, K., Crino, P.B., Gorter, J.A., Nellist, M., Jansen, F.E., Spliet, W.G.M., Rijen, P.C. van, Wittink, F.R.A., Breit, T.M., Troost, D., Wadman, W.J. & Aronica, E. (2010). Gene expression analysis of tuberous sclerosis complex cortical tubers reveals increased expression of adhesion and inflammatory factors. *Brain pathology, 20*(4), 704-719.

Vliet, E.A. van (2010). Gevecht tegen de beschermingsmechanismen van het brein. *TSC Contact, 112*, 26-27.

Vliet, E.A. van (2010). Gevecht tegen de beschermingsmechanismen van het brein. *Episcoop, 3*, 4-6.

Van Dycke, A., Raedt, R., Dauwe, I., Sante, T., Wyckhuys, T., Meurs, A., Vonck, K., Wadman, W. & Boon, P. (2010). Continuous local intrahippocampal delivery of adenosine reduces seizure frequency in rats with spontaneous seizures. *Epilepsia, 51*(9), 1721-1728.

Kalitzin S.N., Velis, D.N., Lopes da Silva, F.H. (2010) Stimulation-based anticipation and control of state transitions in the epileptic brain. Epilepsy Behav. Mar;17(3):310-23.

Proceedings

Holtman, L., Vliet, E.A. van, Edelbroek, P.M., Aronica, E. & Gorter, J.A. (2010). Effects of cox-2 inhibition with SC-58236 on epileptogenesis, seizures and antiepileptic drug therapy with phenytoin. In *7th Forum of European Neuroscience 2010, Amsterdam*. Amsterdam, The Netherlands.

Zurolo, E., Aronica, E., Fluiter, K., Lyer, A., Vreijling, J., Vliet, E.A. van, Baayen, J.C. & Gorter, J.A. (2010). Expression pattern of microRNA-146a in experimental and human temporal lobe epilepsy. In *7th Forum of European Neuroscience 2010, Amsterdam*. Amsterdam, The Netherlands.

Vliet, E.A. van, Holtman, L. & Gorter, J.A. (2010). Effects of statin treatment on the development of epilepsy and blood-brain barrier leakage in epileptic rats. In *7th Forum of European Neuroscience 2010, Amsterdam*. Amsterdam, The Netherlands.

Book Chapter

Wytse J.Wadman (2010). De hersenen, een lerende machine. In Nina Lazeron, Ria van Dinteren, Eds, 2010 BREIN@WORK, Springer pp 51-60.

Membership editorial board

Vliet, E.A. van (Ed.). (2010). *Journal of Neuroscience*.

Vliet, E.A. van (Ed.). (2010). *Acta Neuropathologica*.

Vliet, E.A. van (Ed.). (2010). *Epilepsy Research*.

Vliet, E.A. van (Ed.). (2010). *Epilepsia*.

Prizes

Vliet, E.A. van (2010). The role of the blood-brain barrier and multidrug transporters in pharmacoresistant epilepsy'. Prijs uitgereikt tijdens het Nationaal Epilepsie Symposium: Nieuwegein,

Nederland (2010, May 28 - 2010, May 28). Erkenning.

Other result

Vliet, E.A. van (2010). Gevecht tegen de beschermingsmechanismen van het brein. uitreiking Harry Maynardiprijs .

Invited lectures

Hooft, J.A.van (November 2010). *5-HT3 receptors are growing up: a critical role in cortical development.* Invited lecture at the Department of Cell and Molecular Biology, John A. Burns School of Medicine, University of Hawaii, USA.

Lopes da Silva, F.H. (2010, November 29). *Epilepsies as Dynamical Diseases*. Epilepsie Centrum, Kempenhaeghe, The Netherlands.

Lopes da Silva, F.H. (2010, November 15). *Is it possible to replace artificially some brain functions?.* INESC Workshop. Culturgest. Lisbon, Portugal.

Lopes da Silva, F.H. (2010, November 8). *Brain waves: insights from dynamic models of neuronal networks*. University of Warsaw, Poland.

Lopes da Silva, F.H. (2010, November 5). *The Hippocampal formation system: re-entrant circuits – substrate of memory*. International League Against Epilepsy Task Force, Amsterdam, The Netherlands.

Lopes da Silva, F.H. (2010, October 29). *The sources of Absence seizures: Electrophysiology, hemodynamic signals and computational models*. Brain Science Center, Tohoku University, Sendai, Japan.

Lopes da Silva, F.H. (2010, October 28). *The cellular mechanisms of EEG rhythms*. International Congress of Clinical Neurophysiology. Kobé, Japan.

Lopes da Silva, F.H. (2010, September 24). *Transition to seizure in photosensitve Epilepsy*. Epilepsy Research UK – Preictal Phenomena Expert Workshop. Oxford, UK.

Lopes da Silva, F.H. (2010, September 15). *Epileptogenesis and the Blood-Brain Barrier*. Koninklijke Nederlandse Pharmaceutische Studenten Vereniging. Apeldoorn, The Netherlands.

Lopes da Silva, F.H. (2010, August 18). *Dynamics of Neural Mass Models: EEG/MEG and hemodynamic signals*. 5th International Summer School in Biomedical Engineering, Multimodal integration of functional brain measurements, Lutherstadt-Wittenberg, Germany.

Lopes da Silva, F.H. (2010, April 2). *Dynamics of phase transitions in epilepsies*. Faculté de Médecine, Hôpital La Timmone, Marseille, France.

Lopes da Silva, F.H. (2010, February 2). *Dynamics of Phase transitions in Epilepsies*. Latin-American Summer School on Epilepsy, São Paulo, Brazil.

Lopes da Silva, F.H (2010,February 3). "*Processes mediating epileptogenesis revealed by micro-array analyses and the modulation of specific molecular targets*". Latin-American Summer School on Epilepsy, São Paulo, Brazil.

Wadman, W.J. (2010, May 21). *Neurostimulation, where do we go?* Int.Epilepsy Workshop, Ghent, Belgium

Wadman, W.J. (2010, June 21). *We zijn ons brein*. The magic machine, Museum van der Togt, Amstelveen

Wadman, W.J. (2010, July 2). *Deep Brain Stimulation as therapeutic alternative.* FENS, Amsterdam

Wadman, W.J. (2010, August 7). *Brain@Work*. Van Ditmar, Amsterdam

Wadman, W.J. (2010, September, 22). *Integrated data analysis*, Scientifica, Maidenhead, Engeland

Wadman, W.J. (2010, September, 24). *The future of Neuroscience*. Dean special session, Ghent, Belgium

Wadman, W.J. (2010, September 23). *Endocannabinoid mediated modulation of synaptic transmission at cell and network level in the PFC*. TIPharma, Weesp

Wadman, W.J. (2010, November 4). *De hersenen en EM-velden*. Antenne Vereniging, Utrecht

Wadman, W.J. (2010, November 28). *(Anti)-epileptogenesis from a neurophysiological viewpoint.* Kempenhaeghe Symposium, Eindhoven

Wadman, W.J. (2010, December 9). University Maastricht

Wadman, W.J. (2010, December 9). *Extracellular Field recordings. Plasticity, PTP, LTP, LTD & STDP*. University Maastricht

Structural and functional plasticity of the nervous system

PhD Theses

Maas, C (2010, September 10). *Molecular regulation of death receptor- and DNA damage-induced apoptosis.* UvA Universiteit van Amsterdam (134 pag.). Prom./coprom.: prof.dr. J. Borst.

Oomen, C.A. (2010, June 04). *Shaping the brain through experience. Effects of stressful live events on hippocampal neurogenesis, morphology and function.* UvA Universiteit van Amsterdam (204 pag.) (Amsterdam). Prom./coprom.: prof.dr. M. Joels, prof.dr. P.J. Lucassen & dr. H.J. Krugers.

Peperzak, L. (2010, February 12). *Molecular mechanisms underlying CD27-CD70 costimulation.* UvA Universiteit van Amsterdam (161 pag.). Prom./coprom.: prof.dr. J. Borst.

Academic publications

Kaminsky, Y.G., Marlatt, M.W., Smith, M.A. & Kosenko, E.A. (2010). Subcellular and metabolic examination of amyloid-beta peptides in Alzheimer disease pathogenesis: evidence for Abeta(25-35). *Exp Neurol.*, 221(1), 26-37.

Krugers, H.J., Lucassen, P.J., Karst, H. & Joëls, M. (2010). Chronic stress effects on hippocampal structure and synaptic function: relevance for depression and normalization by anti-glucocorticoid treatment. *Frontiers in Synaptic Neuroscience, 2*(24), 24.

Lucassen, P.J., Meerlo, P., Naylor, A.S., Dam, A.M. van, Dayer, A.G., Fuchs, E., Oomen, C.A. & Czéh, B. (2010). Regulation of adult neurogenesis by stress, sleep disruption, exercise and inflammation: Implications for depression and antidepressant action. *European Neuropsychopharmacology, 20*(1), 1-17.

Wirths, O., Bethge, T., Marcello, A., HarMayer, A., Jawhar, S., Lucassen, P.J., Multhaup, G., Brody, D.L., Esparza, T., Ingelsson, M., Kalimo, H., Lannfelt, L. & Bayer, T.A. (2010). Pyroglutamate Abeta pathology in APP/PS1KI mice, sporadic and familial Alzheimer's disease cases. *Journal of Neural Transmission, 117*(1), 85-96.

Marlatt, M.W. & Lucassen, P.J. (2010). Neurogenesis and Alzheimer's disease: biology and pathophysiology in mice and men. *CURR ALZHEIMER RES, 7*(2), 113-125.

Marlatt, M.W., Lucassen, P.J. & Praag, H. van (2010). Comparison of neurogenic effects of fluoxetine, duloxetine and running in mice. *Brain Research, 1341*, 93-99.

Lucassen, P.J., Stumpel, M.W., Wang, Q. & Aronica, E. (2010). Decreased numbers of progenitor cells but no response to antidepressant drugs in the hippocampus of elderly depressed patients. *NEUROPHARMACOLOGY, 58*(6), 940-949.

Christensen, D.Z., Schneider-Axmann, T., Lucassen, P.J., Bayer, T.A. & Wirths, O. (2010). Accumulation of intraneuronal Aβ correlates with ApoE4 genotype. *Acta Neuropathologica, 119*(5), 555-566.

Oomen, C.A., Soeters, H., Audureau, N., Vermunt, L., Hasselt, F.N. van, Manders, E.M.M., Joëls, M., Lucassen, P.J. & Krugers, H. (2010). Severe early life stress hampers spatial learning and neurogenesis, but improves hippocampal synaptic plasticity and emotional learning under high-stress conditions in adulthood. *Journal of Neuroscience, 30*(19), 6635-6645.

Karst, H., Berger, S., Erdmann, G., Schütz, G. & Joëls, M. (2010). Metaplasticity of amygdalar responses to the stress hormone corticosterone. *Proceedings of the National Academy of Sciences of the United States of America, 107*(32), 14449-14454.

Krugers, H.J., Hoogenraad, C.C. & Groc, L. (2010). Stress hormones and AMPA receptor trafficking in synaptic plasticity and memory. *Nature Reviews. Neuroscience, 11*(10), 675-681.

Henckens, M.J.A.G., Wingen, G.A. van, Joëls, M. & Fernández, G. (2010). Time-dependent effects of corticosteroids on human amygdala processing. *Journal of Neuroscience, 30*(38), 12725-12732.

Luo, L., Rodriguez, E., Jerbi, K., Lachaux, J.P., Martinerie, J., Corbetta, M., Shulman, G.L., Piomelli, D., Turrigiano, G.G., Nelson, S.B., Joëls, M., Kloet, E.R. de, Holsboer, F., Amodio, D.M., Frith, C.D., Block, M.L., Zecca, L., Hong, J.S., Dantzer, R., Kelley, K.W. & Craig, A.D. (2010). Ten years of Nature Reviews Neuroscience: insights from the highly cited. *Nature Reviews. Neuroscience, 11*(10), 718-726.

Zhou, M., Bakker, E.H.M., Velzing, E., Berger, S., Oitzl, M., Joëls, M. & Krugers, H.J. (2010). Both mineralocorticoid and glucocorticoid receptors regulate emotional memory in mice. *Neurobiology of Learning and Memory, 94*(4), 530-537.

Yehuda, R., Joëls, M. & Morris, R.G.M. (2010). The memory paradox. *Nature Reviews. Neuroscience, 11*(12), 837-839.

Stegeren, A.H. van, Roozendaal, B., Kindt, M., Wolf, O.T. & Joëls, M. (2010). Interacting noradrenergic and corticosteroid systems shift human brain activation patterns during encoding. *Neurobiology of Learning and Memory, 93*(1), 56-65.

Bruel-Jungerman, E., Lucassen, P.J. & Francis, F. (2010). Cholinergic influences on cortical development and adult neurogenesis. *Behavioural Brain Research*.

Book Chapters

Lucassen, P.J., Fitzsimons, C.P., Vreugdenhil, E., Hu, P., Oomen, C., Revsin, Y., Joëls, M. & Kloet, E.R. de (2011). Regulation of structural plasticity and neurogenesis during stress and diabetes; protective effects of glucocorticoid receptor antagonists. In A.G. Gravanis & S.H. Mellon (Eds.), *Hormones in neurodegeneration, neuroprotection, and neurogenesis* (pp. 103-120). Weinheim, Germany: Wiley-VCH.

Membership editorial board

Lucassen, P.J. (Ed.). (2010). *Translational Neuroscience*.

Lucassen, P.J. (Ed.). (2010). *Frontiers in Neurogenesis*.

Invited lectures

Fitzsimons, C. (2010, July). *Early life stress, microRNAs and healthy aging.* Dept Neurosciences and brain Technologies, Italian Institute of Technology, Genua, Italy.

Korosi, A. (2010, August). *Resilience to stress-related disorders as a result of augmented maternal care involves reduced excitation onto CRH expressing neurons in the hypothalamus.* 7th World Congress on Stress. Leiden, the Netherlands.

Lucassen, P.J. (2010, September 30). *Neurogenesis in Alzheimer (models).* Bordeaux, France, Invited Lecture at the INSERM Neurogenesis Meeting.

Lucassen, P.J. (2010, October 14). *Stress and new brain cells.* Utrecht, The Netherlands, Invited Lecture at the Dutch Publieksdag of the Dutch Brain Foundation.

Lucassen, P.J. (2010, August 31). *Alzheimer's disease: neurogenesis and enriched environment; promising avenues?* Amsterdam, The Netherlands, Lecture at the ECNP Brain stoming session.

Lucassen, P.J. (2010, May 20). *Structural plasticity in relation to (early) stress and depression.* New Castle, U.K, Invited lecture at the Institute for Neuroscience and Academic Psychiatry, Medical School.

Lucassen, P.J. (2010, March 15). *Structural plasticity in dementia.* Amsterdam, the Netherlands, Lecture at the International NEURAD meeting.

Lucassen, P.J. (2010, January 25). *Stem cells in the adult brain.* Groningen, The Netherlands, invited lecture Graduate School BCN.

Lucassen, P.J. (2010, November 11). *Mouse models for Alzheimer; where have we come from and are we there yet?* San Diego, USA, Invited Lecture at the ISAO workshop.

Lucassen, P.J. (2010, November 10). *"Alzheimer's disease 2011; the state of affairs".* San Dïego, USA, Plenary introductory lecture for the ISAO Alzheimer workshop.

Krugers, H.J. (2010, March 10). *Slim door stress?* Amsterdam, The Netherlands, invited lecture at the IICS Symposium.

Krugers, H.J. (2010, July 06). *Glucocorticoid regulation of synaptic efficacy and plasticity.* Amsterdam, The Netherlands, Invited lecture at the FENS Forum.

Krugers, H.J. (2010, November 24). *Stress hormone effects on Cognitive Performance.* Utrecht, The Netherlands, Invited lecture at NWO Cognition symposium.

Krugers, H.J. (2010, December 13). *Molecular Regulation of Fearful memories.* Groningen, The Netherlands, Invited lecture at RU Groningen.

Krugers, H.J. (2010, December 15). *Stress hormones, synapses and memory.* Amsterdam, The Netherlands, CSCA Lecture.

Krugers, H.J. (2010, November 09). *Het belang van ouderlijke zorg: over rol en ontwikkeling van het geheugen: Hersenen, hechting en hulpverlening.* Amsterdam, The Netherlands, Lecture at Symposium.

Appendix 4

Research programme **Life Science Technologies**

Mass Spectrometry of Biomacromolecules

PhD Theses

Nessen, M. (2010, December 10). *Development of an enrichment method for azide-containing peptides to study proteome dynamics by mass spectrometry.* UvA Universiteit van Amsterdam (132 pag.). Prom./coprom.: prof.dr. C.G. de Koster, prof.dr. H. Hiemstra, dr. L. de Jong & dr. J.H. van Maarseveen.

Academic publications (refereed)

Sorgo, A.G., Heilmann, C.J., Dekker, H.L., Brul, S., Koster, C.G. de & Klis, F.M. (2010). Mass spectrometric analysis of the secretome of Candida albicans. *Yeast, 27*(8), 661-672.

Backhaus, K., Heilmann, C.J., Sorgo, A.G., Purschke, G., Koster, C.G. de, Klis, F.M. & Heinisch, J.J. (2010). A systematic study of the cell wall composition of Kluyveromyces lactis. *Yeast, 27*(8), 647-660.

Boer, A.D. de, Groot, P.W.J. de, Weindl, G., Schaller, M., Riedel, D., Diez-Orejas, R., Klis, F.M., Koster, C.G. de, Dekker, H.L., Gross, U., Bader, O. & Weig, M. (2010). The Candida albicans cell wall protein Rhd3/Pga29 is abundant in the yeast form and contributes to virulence. *Yeast, 27*(8), 611-624.

Invited lectures

Koster, C.G. de (2010, October 04). *Classical and high-throughput proteomics.* Amsterdam, 5th FINSysB Training Course.

Heilmann, C.J. (2010, November 01). *Quantitative strategies to map the Candida albicans cell wall proteome.* Lunteren, NWO/CW Anal.Scheikunde.

Koster, C.G. de (2010, October 28). *Ten years of mass spectrometry of the microbial cell surface proteome at the Swammerdam Inst.for Life Sciences.* Amsterdam, Ned.Ver.voor Massaspectrometrie.

Koster, C.G. de (2010, January 27). *Identification and quantitation of newly synthesized proteins in Escherichia coli.* Brugge, Belgie, 11th Int.Symposium on Hyphenated Techniques in Chromatography and Hyphenated Chrom.Analyzers.

Heilmann, C.J. (2010, December 06). *Quantitative strategies to map the Candida albicans cell wall proteome.* Veldhoven, NWO/CW Studiegroep Eiwitten.

BioSystems Data Analysis

PhD Theses

Vis, D.J. (2010, November 02). *Endocrine dynamics.* UvA Universiteit van Amsterdam (141 pag.). Prom./coprom.: prof.dr. A.K. Smilde, J. van der Greef & dr. J.A. Westerhuis.

Rubingh, C.M. (2010, November 09). *Real-life metabolomics data analysis: how to deal with complex data?* UvA Universiteit van Amsterdam (144 pag.). Prom./coprom.: prof.dr. A.K. Smilde.

Velzen, E.J.J. van (2010, November 30). *Nutrikinetics.* UvA Universiteit van Amsterdam (177 pag.). Prom./coprom.: prof.dr. A.K. Smilde & dr. J.A. Westerhuis.

Academic publications

Stanimirovic, O., Hoefsloot, H.C.J. & Smilde, A.K. (2010). Optimal measurement design for monitoring batch processes. *AICHE Journal, 56*(3), 837-840.

Zakrzewska, A., Boorsma, A., Beek, A. ter, Hageman, J.A., Westerhuis, J.A., Hellingwerf, K.J., Brul, S., Klis, F.M. & Smits, G.J. (2010). Comparative analysis of transcriptome and fitness profiles reveals general and condition-specific cellular functions involved in adaptation to environmental change in Saccharomyces cerevisiae. *Omics, 14*(5), 603-614.

Westerhuis, J.A., Velzen, E.J.J. van, Hoefsloot, H.C.J. & Smilde, A.K. (2010). Multivariate

paired data analysis: multilevel PLSDA versus OPLSDA. *Metabolomics, 6*(1), 119-128.

Smilde, A.K., Westerhuis, J.A., Hoefsloot, H.C.J., Bijlsma, S., Rubingh, C.M., Vis, D.J., Jellema, R.H., Pijl, H., Roelfsema, F. & Greef, J. van der (2010). Dynamic metabolomic data analysis: a tutorial review. *Metabolomics, 6*(1), 3-17.

Van Mechelen, I. & Smilde, A.K. (2010). A generic linked-mode decomposition model for data fusion. *Chemometrics and Intelligent Laboratory Systems, 104*(1), 83-94.

Vis, D.J., Westerhuis, J.A., Hoefsloot, H.C.J., Pijl, H., Roelfsema, F., Greef, J. van der & Smilde, A.K. (2010). Endocrine pulse identification using penalized methods and a minimum set of assumptions. *American journal of physiology. Endocrinology and metabolism, 298*(2), E146-E155.

Xu, C.J., Hoefsloot, H.C.J., Dijkstra, M., Havenga, K., Roelofsen, H., Vonk, R.J. & Smilde, A.K. (2010). Computational modeling of the human serum proteome response to colon resection surgery. *Analytica Chimica Acta, 661*(1), 20-27.

Christin, C., Hoefsloot, H.C.J., Smilde, A.K., Suits, F., Bischoff, R. & Horvatovich, P.L. (2010). Time alignment algorithms based on selected mass traces for complex LC-MS data. *Journal of Proteome Research, 9*(3), 1483-1495.

Erk, M.J. van, Wopereis, S., Rubingh, C., Vliet, T. van, Verheij, E., Cnubben, N.H.P., Pedersen, T.L., Newman, J.W., Smilde, A.K., Greef, J. van der, Hendriks, H.F.J. & Ommen, B. van (2010). Insight in modulation of inflammation in response to diclofenac intervention: a human intervention study. *BMC Medical Genomics, 3*, 5.

Jansen, J.J., Smit, S., Hoefsloot, H.C.J. & Smilde, A.K. (2010). The photographer and the greenhouse: how to analyse plant metabolomics data. *Phytochemical analysis, 21*(1), 48-60.

Klarenbeek, P.L., Tak, P.P., Schaik, B.D.C. van, Zwinderman, A.H., Jakobs, M.E., Zhang, Z., Kampen, A.H.C. van, Lier, R.A.W. van, Baas, F. & Vries, N. de (2010). Human T-cell memory consists mainly of unexpanded clones. *Immunology letters, 133*(1), 42-48.

Membership editorial board

Kampen, A.H.C. van (Ed.). (2010). *Advances in Bioinformatics*.

Smilde, A.K. (Ed.). (2010). *Journal of Chemometrics*.

Westerhuis, J.A. (Ed.). (2010). *Journal of Chemometrics*.

Westerhuis, J.A. (Ed.). (2010). *Metabolomics*.

Invited lectures

Smilde, A.K. (2010, September 02). *Analyzing metabolomics data: from simple to complex.* Vienna, Austria, University of Vienna.

Smilde, A.K. (2010, September 01). *Extracting systems biology information from complex metabolomics data.* Potsdam, Germany, Max Planck Institute.

Smilde, A.K. (2010,). *Probing systems biology concepts by metabolomics.* Birmingham, U.K., University of Birmingham.

Smilde, A.K. (2010, November 17). *A history of multiblock methods.* Newark,N.J., USA, University of Newark, New York.

Smilde, A.K. (2010, June 15). *Complex metabolomics data generates high-quality systems biology information.* Granada, Spain, Colloquium Mediteranicum Chemometricum.

Micro Array Department and Integrated Bioinformatics Unit

Academic publications (refereed)

Swain, S., Wren, J.F., Stürzenbaum, S.R., Kille, P., Morgan, A.J., Jager, T., Jonker, M.J., Hankard, P.K., Svendsen, C., Owen, J., Hedley, B.A., Blaxter, M. & Spurgeon, D.J. (2010). Linking toxicant physiological mode of action with induced gene expression changes in Caenorhabditis elegans. *BMC Systems Biology, 4*, 32.

Rauwerda, H., Jong, M. de, Leeuw, W.C. de, Spaink, H.P. & Breit, T.M. (2010). Integrating heterogeneous sequence information for transcriptome-wide microarray design; a Zebrafish example. *BMC Research Notes, 3*, 192.

Brunner, J., Wittink, F.R.A., Jonker, M.J., Jong, M. de, Breit, T.M., Laine, M.L., Soet, J.J. de & Crielaard, W. (2010). The core genome of the anaerobic oral pathogenic bacterium Porphyromonas gingivalis. *BMC Microbiology, 10*, 252.

Boer, K., Crino, P.B., Gorter, J.A., Nellist, M., Jansen, F.E., Spliet, W.G.M., Rijen, P.C. van, Wittink, F.R.A., Breit, T.M., Troost, D., Wadman, W.J. & Aronica, E. (2010). Gene expression analysis of tuberous sclerosis complex cortical tubers reveals increased expression of adhesion and

inflammatory factors. *Brain pathology, 20*(4), 704-719.

Bruning, O., Yuan, X., Bruins, W., Oostrom, C.T. van, Rauwerda, J., Wittink, F.R.A., Jonker, M.J., Vries, A. de & Breit, T.M. (2010). Serious complications in gene-expression studies with stress perturbation: An example of UV-exposed p53-mutant mouse embryonic fibroblasts. *Transcription, 1*(3), 159-164.

Melis, J.P., Hoogervorst, E.M., Oostrom, C.T. van, Zwart, E., Breit, T.M., Pennings, J.L., Vries, A. de & Steeg, H. van (2010). Genotoxic exposure: novel cause of selection for a functional ΔN-p53 isoform. *ONCOGENE*.

Jong, M. de, Rauwerda, H., Bruning, O., Verkooijen, J., Spaink, H.P. & Breit, T.M. (2010). RNA isolation method for single embryo transcriptome analysis in zebrafish. *BMC Research Notes, 3*(1), 73.

Broeke-Smits, N.J.P. ten, Pronk, T.E., Jongerius, I., Bruning, O., Wittink, F.R., Breit, T.M., Strijp, J.A.G. van, Fluit, A.C. & Boel, C.H.E. (2010). Operon structure of Staphylococcus aureus. *Nucleic Acids Research, 38*(10), 3263-3274.

Stockhammer, O.W., Rauwerda, H., Wittink, F.R., Breit, T.M., Meijer, A.H. & Spaink, H.P. (2010). Transcriptome analysis of Traf6 function in the innate immune response of zebrafish embryos. *MOL IMMUNOL, 48*(1-3), 179-190.

Pouw, N., Treffers-Westerlaken, E., Kraan, J., Wittink, F., Hagen, T. ten, Verweij, J. & Debets, R. (2010). Combination of IL-21 and IL-15 enhances tumour-specific cytotoxicity and cytokine production of TCR-transduced primary T cells. *Cancer immunology and immunotherapy, 59*(6), 921-931.

Proceedings

Wassink, I., Ooms, M., Neerincx, P., Veer, G. van der, Rauwerda, J., Leunissen, J.A.M., Breit, T.M., Nijholt, A. & Vet, P. van der (2010). e-BioFlow: Improving Practical Use of Workflow Systems in Bioinformatics. In S. Khuri, L. Lhotská & N. Pisanti (Eds.), *Information, Technology in Bio- and Medical Informatics, ITBAM 2010 Vol. 6266. Lecture Notes in Computer Science*. Berlin: Springer.

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