

Group leader: Roel Bovenberg

Group name: Metabolic Pathway Engineering & Screening

Location: DSM Life Science Products, Delft

Web page:

E-Mail: Roel.Bovenberg@dsm.com

Phone:

Relevant research interests:

- bij DSM is de belangstelling voor "Systems Biology" sterk groeiende
- gebaseerd op onze jarenlange ervaring met Metabole Engineering van
- microbiele produktie systemen enerzijds
en snelle ontwikkelingen op het gebied van Genoomanalyse en BioIT
- anderzijds
- beide activiteiten zijn speerpunten in ons lange termijn onderzoek
- en worden intensief met externe partners ontwikkeld en beoefend

Current system biology activities:

-Intern zijn wij bezig een DSM platform voor Systems Biology te formeren, waarin integratie van kennis en vaardigheden uit verschillende projecten en systemen gecoördineerd wordt

- Voorbeelden van door ons gebruikte systemensystemen: *S. cerevisiae*, *E coli*, *Aspergillus niger*, *Penicillium chrysogenum*, *Propionibacterium*, *Streptomyces clavuligerus*, tbv productie van eiwitten, metabolieten, biomassa,

- In alle gevallen is sprake van permanente optimalisatie van bestaande bioprocessen en daarin gebruikte micro-organismen

- Daarnaast zien we stijgende aantal compleet nieuwe biosynthese processen door toepassing van Metabole Pathway Engineering technieken

- Alles bij elkaar opgeteld beschikken we intern inmiddels over een behoorlijke groep ervaren onderzoekers met elkaar overlappende expertisegebieden (van basale genetica t/m proces technologen en modeleurs) + benodigde equipment om tot relevant en kwalitatief goed onderzoek op dit gebied te komen.

Relevant collaborations (e.g.):

Internationaal hebben we goede contacten op dit gebied in Duitsland, Denemarken en de USA en oa met de voormalige UEF (ME conferences)

Group leader: Stanley Brul

Group name: Molecular Biology & Microbial Food Safety SILS (co-sponsored University Chair 50% UvA, 50% Unilever Research & Deveelopment):

Other staff members involved: Hans van der Spek (UD), Gertien Smits (UD), Marian de Jong (technician UvA), Femke Mensonides (PhD -end 2003)/ Pepijn Boeree PhD (2007), Alex ter Beek PhD (2006), Martha Arthal Sanz PhD (2004), Esther Willems technician (2004), Andrea O'Brien Post-doc (STW 2006), Bart Keijser (EET 2005), Sharon Mithoe (technician EET 2005), Catarina Resende (Marie-Curie EU 2004)

Location: Swammerdam Institute for Life Sciences, BCA, University of Amsterdam

Web page: <http://www.science.uva.nl/research/sils>

E-Mail: brul@science.uva.nl

Phone: 31-20-5257079; mobile:31-0651378726; fax: 31-20-5256971

Relevant research interests:

The interaction between microorganisms and their environment studied at the cellular level using in particular novel genomics tools. Together with the Microbial Physiology Chair at SILS the focus is on studying in an integral way the transcriptome, proteome and metabolome of microbial cells in the context of their (natural) environment. Main model systems are *Bacillus subtilis* and baker's yeast *Saccharomyces cerevisiae*. In the former we study the behaviour of the general and more specific stress response systems such as the sigmaB regulated system and the sporulation pathway respectively. In *S. cerevisiae* our focus is on an assessment of the response of cells to heat stress and treatment with weak organic acid food preservatives in particular sorbic and benzoic acid. In particular we focus our work together with the microbiology group on the interaction between the antimicrobial compound, its effect on cellular growth, its effect on cellular metabolism and its effect on the signalling status of main cellular stress response pathways. Finally we study genome-wide the events that take place during the lag-phase of growth when microbial cells adapt to new environmental constraints and thus the dynamics of this adaptation may be unveiled. A prime new area is the study of host-pathogen interaction. For the latter we are in the process of developing *Caenorhabditis elegans* as a model host in infection studies with *Salmonella typhimurium* and in particular *Campylobacter jejuni*. Our studies focus on using both genomics approaches towards the identification of host-factors in interacting with the pathogens and at the level of the bacterial pathogens themselves. The views we have on applying systems biology principles in this area are extensively discussed in various recent reviews.

Relevant collaborations (e.g.):

Current collaborations in the Netherlands with respect to applied research focus on application of genomics tools in the understanding of stress resistance of microbial cells in food preservation together with TNO-Food Research, Wageningen University and the Wageningen Centre for Food Sciences, Unilever Research & Development. In addition there are major links with EU groups active in the field of novel preservation techniques and (food) molecular (micro)biology in University College London and Vienna. Recently a framework V project was started as a sub-contractor of Unilever Research & Development, on the mode-of-action and application at low temperatures of high pressure processing was the focal point of study.

Representative publications (possibly links to pdf files):

Klis, FM, Mol P, Hellingwerf KJ and Brul S (2002) Dynamics in cell wall structure in *S. cerevisiae* FEMS Microbiol. Rev. 738,1-18
Brul, S, Coote, P, Oomes, SJC, Mensonides FIC and Klis FM (2002) Physiological action of preservative agent: prospective of use of modern microbiological techniques in assessing microbial behaviour in food preservation Int. J. Food Microbiol. 79, 55-64
Brul, S, Klis, FM, Oomes, SJC, Montijn RC, Schuren FHJ, Coote P, Hellingwerf (200) Detailed process design based on genomics of survivors of food preservation processes Trends Food Sci. Technol. 13, 325-333.

Group leader: Prof. Dr. A.M.C. Emons

Group name: Plant Cell Biology

Location: Wageningen University

Web page:

E-Mail: annemie.emons@wur.nl

Phone: +31 317 484329 (2155 secretary, 4329 fax)

Relevant research interests:

Towards comprehension of the living system: taking the cell's infrastructure as a route
At the system level the cell consists of networks of pathways, motifs, and modules with dynamic relationships. One of these networks is the 'Transportome', the infrastructure of the cell consisting of the cytoskeleton of microtubules and actin filaments as its backbone and the cytoskeleton-binding proteins as its regulators. The transportome organises the cell by

being the transport highway and is receiver of topological signals. The infrastructure determines when cell processes occur where, an organisational regulation as vital for cells as for human society. My research focuses on the role of the transportome in plant cell division, elongation and cell wall formation. Research in my group and collaboration with (theoretical) physicists are opening up the possibilities to understand physical aspects of cell infrastructure and its regulation by combining *in vivo*, *in vitro* and *in silico* approaches.

Current system biology activities:

In the systems biology approach all available data about collective properties arising from the properties of the underlying components and their interactions are quantified and used to make mathematical models that can be solved to predict the behaviour of those molecules in various cellular circumstances. The geometrical cell wall model that we have made (Emons 1994, Plant Cell Environment) and worked out together with theoretical physicist professor B.M. Mulder (Emons and Mulder 1998 PNAS, Mulder and Emons 2001 J. Math. Biol.), and applied (Emons et al. 2002, Plant Biology), is one of the first 'System' models in plant cell biology. It addresses the question of cellulose organisation in the cell wall and predicts wall architecture from the number of active cellulose synthases in the plasma membrane.

Group leader: Klaas J. Hellingwerf

Group name: Molecular Microbial Physiology

Other group staff members: Crielaard, Teixeira de Mattos, Klis

Location: Swammerdam Institute for Life Sciences, BCA, University of Amsterdam

Web page: <http://bioicrs6.chem.uva.nl/microbio/index.html>, <http://www.science.uva.nl//sils/>

E-Mail: khelling@science.uva.nl

Phone: +31 20 5257055

Relevant research interests:

In the research group **Molecular Microbial Physiology** (SILS, UvA; staff members: Crielaard, Teixeira de Mattos, Klis and Hellingwerf) the central research topic is the molecular basis of adaptation of microorganisms to (stress) signals from their environment. These studies cover the (sub)molecular and (inter)cellular levels. As stress signals we use e.g. (UV) light, high-temperature, weak acid preservatives, nutrient limitation, etc. Part of this work is very chemically (i.e. molecularly) oriented in the sense that we try to understand the rearrangements within molecules that are required for these responses. At the other extreme we try to understand how this responsiveness helps organisms to increase their evolutionary competitiveness in the environment.

Current system biology activities:

At the central level in our research, therefore, we try to generate an overview of the mechanisms and pathways that are available for responses and adaptation, in a limited number of strategically chosen model organisms (like *Escherichia coli*, *Bacillus subtilis* and *Saccharomyces cerevisiae*). In addition to that, we want to understand how these pathways **interact**, to jointly generate the phenotype of an organism, as it is observable in a model system like the chemostat and/or in the natural environment. In other words, in this part of our research program we try to understand the rationale of why physiology and adaptation is organized the way it is. We consider this the heart of 'systems biology'.

On basis of the info above my estimate is that more than half of our efforts are within the area of 'systems biology'. We tackle the challenges and problems in this area with the tools of biochemistry, physiology, molecular genetics and bioinformatics. I think that additional expertise at the level of mathematics and statistical physics is required to significantly increase the quality of future work in this field. The work of Uri Alon (Weizmann Institute) is a good example of how and in which direction this field is, and will be further, progressing.

Group leader: Frank Holstege

Group name: Genomics Laboratory

Other staff members involved:

Location: University Medical Center Utrecht

Web page:

E-Mail: f.c.p.holstege@med.uu.nl

Phone: +31 30 2538186; fax +31 30 2539035

Relevant research interests:

De onderzoeksgroep die ik in Utrecht aan het opzetten ben werkt aan genoom-brede ontrafeling van transcriptieregulatie mechanismen. We hebben een aantal projecten (deels voortzetting van mijn postdoc werk in VS) die zeer goed passen binnen een systems benadering van regulatie processen.

Current system biology activities:

Binnen eventueel te vormen netwerken kunnen wij in ieder geval onze microarrays beschikbaar maken. Ze zijn ontwikkeld om accuraat veranderingen weer te geven (dankzij optimalisatie van protocollen mbv externe controles) en ze zijn in staat om grote of ongebalanceerde mRNA populatie veranderingen te meten. Hiernaast kunnen wij ook inbrengen onze recente ervaringen met interactie-screening alsook ervaringen met het combineren van verschillende soorten genoom-brede datasets.

Group leader: Adriaan B Houtsmuller

Group name: Department of Pathology

Other staff members: Wim Vermeulen, Jan Hoeijmakers, Roland Kanaar

Location: Josephine Nefkens Institute, Erasmus University Rotterdam

Web page:

E-Mail: houtsmuller@path.fgg.eur.nl

Phone: +31 10 4088 456

Relevant research interests:

Computer modelling of cellular processes

At present, enormous amounts of data are being generated by several types of large-scale genomics and proteomics research. Computer-aided analysis methodology ('bioinformatics') for the interpretation of this data is currently an intensively explored area, and co-ordinated efforts are being made in many institutes to install this methodology in bioinformatics core facilities. However, to fully understand, predict (and interfere with) the complexity of cellular (dys)function, further in-depth study of the specific proteins and pathways elucidated with the above approaches is required.

The rapid development of green fluorescent protein (GFP) technology and continuous innovation of digital imaging equipment and quantitative fluorescence assays have revolutionised the study of proteins and protein-protein interactions in living cells. At present, several research groups within the Erasmus MC (and co-operating groups in other institutes) have embarked upon this novel, challenging area of research to explore vital cellular processes including gene transcription regulation, DNA repair and telomere function in the living cell. The research aims at unravelling the reaction mechanisms of these processes and to dissect the nature and order of consecutive reaction steps. In addition, the developed technology offers new opportunities to study (therapeutic) interference with protein function and interactions, opening the way to develop and apply novel (high throughput) screening methodology to find new targets for cancer therapy.

Briefly, in this type of research the dynamic properties of and interactions between fluorescently labeled proteins are determined *in vivo* using time-lapse microscopic imaging and state-of-the-art quantitative fluorescence assays. For translation of the massive amount of complex data (obtained by these *and* other '-omics' approaches) into physical properties of individual protein activities and, most important, for understanding the complexity of multiple protein-protein interactions in different cellular processes ('molecular networks'), and interaction between these processes, computer modelling is indispensable.

Current system biology activities:

The primary goal of our current research in 'systems biology' is to create a computer modelling environment that serves as an interface between experiment-based computer modelling and computer-model-based experiments. This approach is expected to advance our knowledge of 1) the *in vivo* behaviour and interactions of cellular proteins in the context of the processes they are involved in, 2) the interaction/cross-talk between these processes, 3) the molecular changes (eg. by mutations) that affect the proper regulation of these processes, and/or the interaction between these processes, leading to malignant growth, and 4) the action mechanisms of methods to interfere with these (deviant) processes.

Relevant collaborations:

Representative publications (possibly links to pdf files):

1. Houtsmuller A.B., Rademakers S., Nigg A.L., Hoogstraten D., Hoeijmakers J.H.J. and Vermeulen W. Action of DNA repair endonuclease ERCC1/XPF in living cells. *Science* 284, 958-961 (1999).
2. Essers J., Houtsmuller A.B., van Veelen L., Paulusma C., Nigg A.L., Pastink A., Vermeulen W., Hoeijmakers J.H.J. and Kanaar R. Nuclear dynamics of RAD52 group homologous recombination proteins in response to DNA damage. *EMBO J.* 21, 2030-2037 (2002).
3. Hoogstraten D., Nigg A.L., Heath H., Mullenders L.H.F., van Driel R., Hoeijmakers J.H.J., Vermeulen W. and Houtsmuller A.B. Rapid switching of TFIIH between RNA polymerase I and II transcription and DNA repair *in vivo*. *Mol Cell* 10: 1163-1174 (2002).
4. Houtsmuller A.B. and Vermeulen W. Macromolecular dynamics in living cell nuclei revealed by fluorescence redistribution after photobleaching. *Histochem Cell Biol* 5, 13-21 (2001).

Group leader: Klaas Nicolay

Group name: Section of Biomedical NMR, Department of Biomedical Engineering

Location: Eindhoven University of Technology

Web page: <<http://www.bmi2.bmt.tue.nl/nmr/>>

E-Mail: <<mailto:k.nicolay@tue.nl>>

Phone: +31 40 247 5789 / 247 3787

Relevant research interests:

- The regulation of the ATP synthesizing activity of the mitochondrion in skeletal and cardiac muscle in health and disease (diabetes, critical illness, genetic disorders);
- The relation between muscle phenotype (fast-twitch, slow-twitch) and mitochondrial characteristics;
- The use of non-invasive NMR techniques to measure bio-energetic properties, and in particular mitochondrial activity, in muscle in animal models and man;
- The integration of *in vitro* studies on isolated mitochondria, skinned muscle fibers and excised muscles with *in vivo* studies to determine mass flow and concentration control characteristics at different levels of eukaryotic system organization. The combination of molecular biological (transgenic mice), biophysical (NMR) and

modelling techniques to understand adaptive changes in mitochondrial control characteristics in response to gain or loss of enzyme function.

Current system biology activities:

- Biochemical, biophysical and physiological studies of skeletal and cardiac muscle of mice deficient in creatine kinase iso-enzymes. Experimentation and modelling are combined at several *in vitro* and *in vivo* levels of biocomplexity to learn to understand alterations in mitochondrial and muscle phenotype.
- Combined animal model and human studies to measure, understand and therapeutically alter mitochondrial and phenotype muscle in control and diseased states.

Relevant collaborations:

- National:
 - Jeneson (UU)
 - Wagenmakers, Van der Vusse (UM)
 - Van Beek, Krab (VUA)
- International:
 - De Graaf, Rothman (Yale)
 - Walliman (ETH)
 - Wilson (MSU)
 - Gellerich (Halle)

Group leader: Arjen van Ooyen

Group name: Neurons and Networks

Location: Netherlands Institute for Brain Research

Web page:

E-Mail: A.van.Ooyen@nih.knaw.nl

Phone:

Relevant research interests:

Cellular and cytoskeletal mechanisms of neuronal morphogenesis

- How molecular and cellular mechanisms involved in neurite elongation and branching—the dynamics of the actin and microtubule cytoskeletons and their modulators—lead to the generation of dendritic tree morphology.
- The role of the actin and microtubule dynamics in the motility and shape changes (e.g. outgrowth and retraction of filopodia) of growth cones.

Cellular mechanisms for growth cone navigation

- Intracellular mechanisms and signaling networks underlying robust gradient detection by growth cones.
- Integration by the growth cone of multiple guidance cues, such as diffusible chemoattractants and repellents as well as cell- and substrate-bound molecules.

Homeostatic regulation of neuronal excitability

- Intracellular signaling networks underlying the homeostasis of neuronal excitability.

Current system biology activities:

- Building a simulation tool for the modeling of growing neurons and the intracellular mechanisms involved (a collaborative project with the University of Stirling, UK).
- Modeling microtubule dynamics and competitive mechanisms in neurite outgrowth.
- Phenomenological models of neurite elongation and branching.
- Modeling axon guidance and pathfinding (a collaborative project with CWI, Amsterdam).
- Experimental investigations into the role of Rho-signaling in neurite elongation and branching.

Relevant collaborations (e.g.):

Representative publications (possibly links to pdf files):

Group leader: Sasha Panfilov

Group name: Theoretical Biology

Location: Eindhoven University of Technology

Web page:

E-Mail: A.V.Panfilov@bio.uu.nl

Phone: +31-30-2533694

Relevant research interests:

- We are interested in developing of a 'silicon human cardiac cell' and its incorporation to the virtual human heart in order to understand the mechanisms of cardiac arrhythmias and develop new ways (new drugs) for their management.

Current system biology activities:

- Our group is working on development of human cardiac cell models. Recently we have developed one of the first human ventricular cell models (together with D.Noble Oxford), which describes cardiac excitation via 12 ionic gates. We plan to refine this model in near future by better description of ionic currents and by including the description of the metabolism. The metabolism is of great importance for ATP-dependent currents, which play a major role during various cardiac diseases (e.g. ischemia). Some recent experimental data also show importance of gene expression during various cardiological diseases. Hence, we would be interested to include gene regulation processes to our model in future. Our main objective is to develop the best electrophysiological model of human cardiac cell and using computer modeling extend it to the whole organ with the aim to study mechanisms of cardiac arrhythmias in human heart. Note, that the realistic modeling is probably the only possibility to study arrhythmogenesis in human heart, as cardiac arrhythmias involve the whole organ and their experimental and clinical studies are very limited. Thus, we would be also interested if the System Biology program includes not only 'cardiac silicon cell' development but also few applications of that 'cells', which could go beyond the cellular level.

Relevant collaborations:

Possible Dutch collaborations inside this project. On metabolism with Hans Westerhoff. On model development with Physiology of AMC (R. Wilders), on cell connections and arrhythmogenesis with Medical Physiology UMC (former Habo Jongsma group).

Group leader: Mark A. Peletier

Group name: PDEs in the Life Sciences

Other staff members involved: R. Planque (mathematical modelling), Joke Blom, Jason Frank, Johannes Krottje, Nga Pham Thi, Ben Sommeijer, Jan Verwer (all scientific computing)

Location: Centrum voor Wiskunde en Informatica, Amsterdam

Web page: <http://www.cwi.nl/projects/pdels>

E-Mail: peletier@cwi.nl

Phone: +31 20 592 4226 (fax +31 20 592 4199)

Relevant research interests:

Our group focuses on numerical and theoretical analysis of partial differential equations, with an eye on applications in the life sciences. On the numerical side we place the emphasis on

methods that are adaptive in both space and time, allowing us to handle systems with strong spatial gradients and stiff time discretizations. Simultaneously we use and develop theoretical methods to gain qualitative and quantitative understanding of the systems involved.

Current system biology activities:

- * Relation between diffusive gradients, metabolic control analysis, and signal transport (with the Westerhoff group and Kholodenko)
- * Axonal growth cones: relation between local rules and resulting axonal connections (bundling and debundling) (with Van Pelt and Van Ooijen)
- * Continuum models for lipid bilayers
- * Integration of modularity, adaptive simplification, and local particle descriptions into PDE-based simulations (with Kaandorp, Van Schuppen, and the Westerhoff group)

Relevant collaborations (see above):

Representative publications (possibly links to pdf files):

B. Lastdrager, Numerical solution of mixed gradient-diffusion equations modelling axon growth, Technical Report MAS-R0203 Centrum voor Wiskunde en Informatica, P.O. Box 94079, 1090 GB Amsterdam, The Netherlands, January 2002.
Christof Francke, Pieter W. Postma, Hans V. Westerhoff, Joke G. Blom, and Mark A. Peletier, Why the Phosphotransferase System of *Escherichia coli* Escapes the Diffusion Limitation of Signal Transduction, Transport and Metabolism that Confronts Mammalian Cells, CWI Report MAS-R0218 Accepted for publication in Biophys. J.
M.A. Peletier, H.V. Westerhoff, and B.N. Kholodenko, Control of Spatially Heterogeneous and Time-varying Cellular Reaction Networks: A New Summation Law, CWI Report MAS-R0226 Submitted to Biophys. J.
J.G. Blom and M.A. Peletier, A continuum model of lipid bilayers CWI Report MAS-R0229 Submitted to Euro. Jnl of Applied Mathematics.

Group leader: Bert Poolman

Group name: Department of Biochemistry

Location: University of Groningen

Web page: <http://www.chem.rug.nl/enzymology/>

E-Mail: b.poolman@chem.rug.nl

Phone: +31 50 3634190 (secre. 4209; Fax 4165)

Relevant research interests:

Prokaryotic Cell Volume Regulation

A large part of the activities in my group is aimed understanding the regulation of the cell volume in prokaryotes. We have identified the major components involved in osmoregulation in *Lactococcus lactis* (genes have been cloned, relevant knockouts have been constructed, proteins have been purified and studied *in vitro*, e.g., refs. 1 and 2), including transporters, mechanosensitive channel proteins and transcription factors, and we are beginning to understand their osmoregulated activities. The next step is to analyze their activities at the transcriptome and proteome level but also to determine the changes in the lipid component of the cell ('lipidome'). When a cell is confronted with osmotic stress, the cell volume increases (downshift) or decreases (upshift) and this results in changes in the ionic strength and crowdedness of the cytoplasm, factors that influence different steps in the osmoregulation of *L.lactis*.

The next step is to analyze the effect of cellular ionic strength and crowding on the expression and activities of other macromolecules in the cell. The majority of these molecules will not be directly involved in osmoregulation but their function will be affected by the consequences of osmotic stress. There are many indications that under physiologically realistic 'crowded' conditions several cellular components function differently than in diluted aqueous media. Even more dramatic, certain intrinsically disordered proteins gain structure (and activity) under crowded conditions. These systems will be sensitive to osmotic stress

and a systematic genome/proteome-wide and numerical approach is needed to ultimately understand the responses of the cell.

Current system biology activities:

Initial experiments to determine the consequences of osmotic stress at the transcriptome level are underway (together with Oscar Kuipers). Ultrastructural and biochemical analyses of the cell envelope are carried out in parallel; (membrane) proteome studies will follow later. *Why L. lactis?* Relatively simple organism with little redundancy at the genome level; well-established genetics and biochemistry. Realistic possibilities in terms of Systems Biology. *Why cell volume regulation?* Important, generic and well-defined "SubSystems Biology" problem that lends itself to an elucidation of the systems properties.

Relevant collaborations (e.g.):

Representative publications (possibly links to pdf files):

- Heide, T. van der, Stuart, M.C.A., and Poolman, B. (2001) On the osmotic signal and osmosensing mechanism of an ABC transport system for glycine betaine. *EMBO Journal*, **20**, 7022-7032.
2. Poolman, B., Blount, P., Folgering, J., Friesen, R.H.E., Moe, P.C., and Heide van der, T. (2002) How do membrane proteins sense water stress? *Molec. Microbiol.*, **44**, 889-902.

Group leader: Ger van der Vusse

Group name: Dept. of Physiology

Location: Maastricht University

Web page:

E-Mail: Jos.Heemskerk@fys.unimaas.nl

Phone: +31.43.3884003

Relevant research interests: (SEE BELOW)

Current system biology activities:

SYSTEEMBIOLOGISCH ONDERZOEK VAN DE SPIERCEL

Het onderzoek wordt uitgevoerd binnen een samenwerkingsproject van de capgroep Fysiologie, CARIM, UM (prof.dr. G.J. van der Vusse) en de faculteit Electrotechniek TUE (dr.ir. N.A.W. van Riel en prof.dr.ir. P.P.J. van den Bosch).

Het hoofddoel van het project is om de energie- en calciumhuishouding in de hartspiercel mathematisch te modelleren waarbij het model direct gekoppeld wordt aan kwantitatieve experimentele gegevens. Dit resulteert in een modelgebaseerde interpretatie van experimentele data. Hiertoe wordt gebruik gemaakt van Systeem Theoretische principes waarbij onderscheid gemaakt wordt tussen massastromen en informatie. De systeem biologische benadering richt zich op (relatief) compacte beschrijvingen van het dynamisch gedrag door met name de (hiërarchische) regulatie mechanismen te modelleren. Hierbij is kennisgedreven modelreductie van (te) complexe fysiologische modellen essentieel. Er wordt gebruik gemaakt van model analyse technieken zoals modale analyse en Metabolic Control Analysis. Vaak is nog niet alle kwantitatieve informatie beschikbaar om te komen tot een eenduidig model. Binnen de mogelijke modelrealisaties kan een specifiek model geselecteerd worden op basis van additionele kennis in de vorm van randvoorwaarden en (heterologe) experimentele data.

Onder normale omstandigheden is de hartspier voor zijn energie-omzetting afhankelijk van glucose en vetzuren als oxideerbare substraten. Deze substraten worden via de bloedbaan aangevoerd en diffunderen via de endotheellijst en het interstitium naar de cardiomyocyten. Na transport door het plasmamembraan en diffusie door het cytoplasma vindt mitochondriale oxidatie plaats. De transportmechanismen voor glucose (een hydrofiële verbinding) en vetzuur (sterk hydrofoob) verschillen aanzienlijk. Vooral het mechanisme waarmee vetzuren door de hartspier opgenomen en de wijze waarop de mitochondriale oxidatie geregeld wordt is slechts in beperkte mate opgehelderd. Voorts blijkt uit recent

onderzoek dat tal van cardiale ziekten (hypertrofie/falen, diabetische cardiomyopathie) gepaard gaan met veranderingen in de vetzuuroxidatie enerzijds en ophoping van vetzuur anderzijds, hetgeen aanleiding kan zijn tot lipotoxiciteit.

Calcium ionen in het cytoplasma van de cardiomyocyten spelen een essentiële rol bij de mechanische activiteit van het hart. Rhythmische veranderingen in cytoplasmatisch Ca^{2+} (laag tijdens diastole, hoog tijdens systole) maken relaxatie en contractie van de myocyte mogelijk. Ook veranderingen in de calcium homeostase blijken geassocieerd te zijn met tal van cardiomyopathieën.

Momenteel worden mathematische modellen ontwikkeld en geïmplementeerd om de *in situ* kinetische eigenschappen van eiwitten die betrokken zijn bij het instandhouden van de calcium huishouding en de cardiomyocyte te bepalen in het intacte hart en te onderzoeken welke veranderingen opgetreden zijn in de kinetische eigenschappen tijdens hartfalen en diabetische cardiomyopathie. Voorts worden mathematische modellen ontworpen waarmee de opname, transport en oxidatie van vetzuur en glucose in de hartspier wordt gesimuleerd en mogelijke barrières en controlepunten geïdentificeerd en gekwantificeerd worden. Met deze modelmatige benadering zal tevens getracht worden aan te geven in hoeverre veranderingen in het vetzuur- en koolhydraatmetabolisme een causale rol spelen bij de functionele afname in het falende en diabetische hart.

Tevens is het doel om uiteindelijk tot een geïntegreerd model te komen van energiehuishouding en calcium homeostase in de arbeidende cardiomyocyte.

Relevant collaborations:

- Prof.dr.ir. P.P.J. van den Bosch en Dr.ir N.A.W. van Riel, Department of Electrical Engineering, TU/e, NL
- Prof.dr. J.B. Bassingthwaite, Center for Bioengineering, University of Washington, Seattle, USA
- Dr. L. Ligeti, Dept. of Physiology, Semmelweis University, Budapest, Hungary.

Group leader: Hans V. Westerhoff

Group name: Molecular Cell Physiology and Mathematical Biochemistry

Other staff members involved: Barbara Bakker (yeast, trypanosomes), Fred Boogerd (emergence), Klaas Krab (diabetes, modular kinetic analyses), Wilfred Roling (microbial ecology), Jacky L. Snoep (als US, South Africa; Silicon cell), Rob van Spanning (Paracoccus, gene networks and regulation), Henk van Verseveld (microbial ecology)

Location: Centre for Research on BioComplex Systems, BCA, Free University and Swammerdam Institute for Life Sciences, BCA, University of Amsterdam

Web page: http://www.bio.vu.nl/html/cell_phy.html and <http://www.bio.vu.nl/hwconf>

E-Mail: hw@bio.vu.nl

Phone: +31 20 4447230 (+31 20 4447229 fax)

Relevant research interests:

- System Biology: How through multiple interactions macromolecules generate the functional behavior of living cells
- Entering the living cell, i.e. perform quantitative experiments to determine the behavior of macromolecules in living cells
- Principles of control, regulation and non equilibrium thermodynamics and statistical mechanics
- Silicon cell, i.e. computer replica of parts of living cells
- Network-based drug design
- Ecological control analysis, i.e. determine whether control and regulation properties of intracellular pathways also operate in ecosystems
- Integrative and vertical genomics: How genome, transcriptome, proteome, metabolome and physiome together and not individually lead to functioning genomics.
- Integrative bioinformatics
- Tumor system biology

Current system biology activities:

[Cellular Bioinformatics](#), (including [Theoretical Biochemistry](#), [Computational biochemistry](#), and [Mathematical Biochemistry](#), [Mathematical Cell Biology](#), and [Quantitative Biochemistry](#))

[Regulatory Networks](#)

[Entering the Living Cell](#)

[Tumor Cell Biology](#)

[Cell & Environment](#)

Relevant collaborations (e.g.):

- National:
 - Peletier, Blom, van Schuppen (CWI)
 - Kaandorp (UvA)
 - Hellingwerf, Brul (UvA)
 - Jeneson (Utrecht)
 - Nicolay (Eindhoven)
 - Teusink (Wageningen)
- International:
 - Heinrich (Berlin)
 - Snoep (Stellenbosch)
 - Kholodenko (Philadelphia)

Representative publications (possibly links to pdf files):

<http://www.bio.vu.nl/hwconf/papers>

Group leader: **Bé Wieringa.**

Group name: Department of Cell Biology, NCMLS UMCN.

Other Staff members: Jack Fransen (UHD), Ineke van der Zee (UD), Frank Oerlemans (technician), Helma Pluk (post-doc), Edwin Janssen (post-doc), Wieke de Bruin (post-doc), Jan Kuiper (Ph.D.student), Femke Streijger (Ph.D.student).

Location: NCMLS UMCN University Nijmegen.

Web page: www.ncmls.kun.nl

E.mail: b.wieringa@ncmls.kun.nl.

Phone: 31-24-3614329/3614287; Fax: 31-24-3615317.

Relevant research interests:

The cellular energetics network for high-energy phosphoryl (i.e. mainly ATP) transfer in mammalian cells consists of several redundant pathways, in which several glycolytic enzymes, members of the creatine kinase (CK) and adenylate kinase (AK) families of enzymes and nucleoside diphosphate kinases (NDPK) play a determining role. Reactions in this complex network are highly compartmentalized and require delicate coupling between cytosolic and organellar events, with coordinated control of cytoarchitectural arrangements and mitochondrial biogenesis and respiration, in a cell-type and developmental-stage dependent manner. It has now been well established that the individual enzymes in the ~P-transfer network work in close physical and functional association with the systems for cell motility and contraction (muscle, polarized migrating cells), intracellular transport and ion homeostasis (muscle, neural cells) machinery. Moreover, the same network also serves to protect cells against ischemic and anoxic stress and in providing (cancer) cells with specially endowed survival skills.

During the past decade our group has been employing reverse genetic approaches with gene knockout and pharmacological inhibition in cellular and animal models to study the cellular effects of

intrinsic or extrinsic metabolic stress in the ~P transfer network in muscle, brain and cancer cells. Our studies with cDNA arrays, semiquantitative Western blotting, ~P flux measurements and physiological and behavioral analysis with biochemical, cell biological, NMR/MRI procedures have revealed that every perturbation in the large-scale organized energetics network (CK-AK knockout or glycolytic enzyme impairment) results in a cell- and mutation-type dependent multigene/multitranscript/mutiprotein response. Adaptation and remodeling involved (i) regulation at the transcriptional and post-transcriptional level, (ii) changes in the positioning and dynamics of the cytoarchitectural organization, and (iii) rewiring of activity through redundant ~P transfer pathways.

Current system biology activities:

Our present studies focus on the combined use of genomics-proteomics-and metabolomics approaches to unravel the control of regulatory metabolic-status signaling pathways (calcineurin-NFat, AMPK, mTOR and transcriptional co-activator events) that sense the metabolic stress in the ~P transfer network and contribute to the adaptational response. Moreover, we now concentrate on the study of the molecular environment of CK, AK and glycolytic enzymes and the use of quantitative real-time dynamic microscopy imaging methods to follow metabolite (ion) and enzyme behavior, to better understand their role in cellular energetics.

Relevant collaborations: Together with the group of dr. Peter Willems/W.Koopman (Dept. Biochemistry NCMLS, UMCN) we work on a computer modeling environment for quantitative description of changes in calcium-ion homeostasis, protein and organelle (mitochondrial)dynamics, and metabolite (NADH, ATP) distribution modes. At the international level we work together with dr. A.Terzic/P.Dzeja for ~P flux and physiological modeling.

Representative publications:

See www.ncmls.kun.nl dept. Cell Biology for background info and movies.

1. Deursen, J. van, Heerschap, A., Oerlemans, F., Ruitenbeek, W., Jap, P., Laak, H. ter, & Wieringa, B. (1993). Skeletal Muscles of Mice Deficient in Muscle Creatine Kinase Lack Burst Activity. *Cell*, 74, 621-631.
2. Deursen, J. van, Ruitenbeek, W., Heerschap, A., Jap, P., Laak, H. ter, & Wieringa, B. (1994). Creatine kinase (CK) in skeletal muscle energy metabolism: A study of mouse mutants with graded reduction in muscle CK expression. *Proc.Natl.Acad Sci USA* 91, 9091-9095.
3. Steeghs, K., Benders, A., Oerlemans, F., de Haan, A., Heerschap, A., Ruitenbeek, W., Jost, C., van Deursen, J., Perryman, B., Pette, D., Brückwilder, M., Koudijs, J., Jap, P., Veerkamp, J. and Wieringa, B. (1997) Altered Ca²⁺ responses in muscles with combined mitochondrial and cytosolic creatine kinase deficiencies. *Cell* 89, 93-103.
4. Janssen, E., Dzeja, P.P., Oerlemans, F., Simonetti, A.W., Heerschap, A., de Haan, A., Rush, P.S., Terjung, R.R., Wieringa, B. and Terzic, A. (2000) Adenylate kinase 1 gene deletion disrupts muscle energetic economy despite metabolic rearrangement. *EMBO J.* 19, 6371-6381.
5. de Groof, A.J.; Oerlemans, F.T.; Jost, C.R.; Wieringa, B. Changes in glycolytic network and mitochondrial design in creatine kinase-deficient muscles (2001) *Muscle-Nerve*. 24(9): 1188-96.
6. Jost, C., van der Zee, C.E.E.M., in 't Zandt, H.J.A., Oerlemans, F., Verheij, M., Streijger, F., Fransen, J., van Deursen, J., Heerschap, A., Cools, A. and Wieringa, B. (2002) Creatine kinase B-driven energy transfer in the brain is important for habituation and spatial learning behaviour, mossy fibre field size and determination of seizure susceptibility. *Eur. J. Neurosci.* 15, 1692-1706.
7. Janssen, E., de Groof, A., Wijers M, Fransen, J., Dzeja P.P., Terzic A., and Wieringa, B. (2003). Adenylate kinase 1 deficiency induces molecular and structural adaptations to support muscle energy metabolism. *J.Biol.Chem.* 278, in press.