Helmholtz Graduate School 'Molecular Cell Biology'

MDC Medical Systems Biology and BIMSB Groups

SYS BIO GROUPS 2010

The Max Delbrück Centre for Molecular Medicine (MDC)

MDC Communication Centre

The MDC is a leading research institution in the field of Molecular Medicine with around 400 publications in top international journals every year, including contributions to Science, Nature, Cell etc. It has more than 50 research groups, an exceptional research base and state-of-the-art facilities, a long-standing cooperation between basic researchers, clinical scientists and the partner universities, and can thus provide excellent training of future scientists in molecular cell biology.

The four major research areas of the MDC are: **Cancer, Cardiovascular and Metabolic Diseases, Function and Dysfunction of the Nervous System and Medical Systems Biology**.

This brochure presents our **Medical Systems Biology research groups** and provides an introduction to the staff attached to the Berlin Institute for Medical Systems Biology and their research interests. It is intended as a starting point for further exploration of our project and research agenda.

Comprehensive publication records for our staff can be found on the Pubmed database: http://www.ncbi.nlm.nih.gov/pubmed/

Please see the last page of this brochure for contact details of the PhD Programme coordinators.

The Helmholtz Graduate School 'Molecular Cell Biology' (HGS-MCB)

The MDC established the Helmholtz Graduate School 'Molecular Cell Biology' (HGS-MCB) in 2007 to offer a unified interdisciplinary platform for structured PhD training at the MDC and its partners. We work in collaboration with our partners the Humboldt-Universität zu Berlin (HU), the Freie Universität Berlin (FU), and the Leibniz Institute for Molecular Pharmacology (FMP). There are currently about 200 international PhD students in the Helmholtz Graduate School selected on competitive basis. For more information please visit www.mdc-berlin.de/phd.

The Graduate School furthermore offers the following **central services**:

- Travel & Collaboration Fund
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- PhD Project Committee
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- Assistance with the registration at the partner universities and organisation of your PhD examination
- Social activities to make your life in one of the most vibrant and affordable of European capitals a truly stimulating and enjoyable experience!

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Wei Chen	P. 3
Christoph Dieterich	P. 4
Stefan Kempa	P. 5
Markus Landthaler	P. 6
Nikolaus Rajewsky	P. 7
Matthias Selbach	P. 8
Jana Wolf	P. 9
Contact details of the Graduate Team	P. 10

MDC Campus

Novel sequencing technology miRNA regulation and human molecular genetics

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The recent introduction of massive parallel sequencing technology has revolutionized genomic research. These so-called next generation sequencing platforms, such as Roche/454, Illumina/solexa and ABI/Solid system can sequence DNA orders of magnitude faster and at much lower cost than conventional Sanger method. With their incredible sequencing capacity, my lab has been focused on developing and implementing various genomic assays to facilitate medical systems biology research. We are now applying the assays in studying transcriptional and posttranscriptional regulation of miRNA genes, as well as identifying genetic factors underlying human diseases

Publications:

Fu X, Fu N, Guo S, Yan Z, Xu Y, Hu H, Menzel C, Chen W*, Li Y, Zeng R, Khaitovich P*. (2009). Estimating accuracy of RNA-Seq and microarrays with proteomics. BMC Genomics. 10, 161-169

Ender C, Krek A, Friedländer MR, Beitzinger M, Weinmann L, Chen W, Pfeffer S, Rajewsky N, Meister G. (2008). A Human snoRNA with MicroRNA-Like Functions.
Mol Cell. 32(4), 519-528

Kuss AW, Chen W. (2008) MicorRNAs in brain function and disease. Curr Neurol Neurosci Rep. 3, 190-197.

Friedländer MR, Chen W, Adamidi C, Maaskola J, Einspanier R, Knespel S, Rajewsky N. (2008). Discovering microRNAs from deep sequencing data using miRDeep. Nat Biotechnol. 26(4), 407-415.

Chen W, Kalscheu V, Tzschach A, Menzel C, Ullmann R, Schulz M, Erdogan F, Li N, Kijas Z, Arkesteijn G, Pajares IL, Goetz-Sothmann M, Heinrich U, Rost I, Dufke A, Grasshoff U, Glaeser BG, Vingron M, Ropers HH.(2008) Mapping translocation breakpoints by next-generation sequencing. Genome Res. 18: 1143-1149

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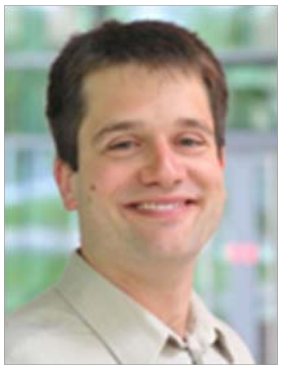
Bioinformatics in Quantative Biology



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Bioinformatics is a highly dynamic discipline, which operates at the interface of life sciences, computer science and formal sciences. Currently, emerging technologies in nucleic acids sequencing, mass spectrometry and imaging revolutionize biology. For the first time, a holistic quantification of biological systems at the level of genomes, transcripts, proteins and metabolites is in reach. Bioinformatics supports this technology-driven transition of biology into a truly quantitative science.

We use existing and develop novel methods for high-throughput data acquisition, processing, model building and inference. Computational studies are backed up by experimental work on nematodes within our group and within active collaborations.

Our main research interests are centered around the following topics: Genome Evolution (e.g. the evolution of parasitism) Quantitative molecular analysis of ecological interactions Biological Sequence Analysis - Motifs, enhancers and long-range genome interactions

Publications:

Dieterich, C. & Sommer, R. J. (2009), 'How to become a parasite - lessons from the genomes of nematodes.', Trends Genet 25(5), 203--209.

Dieterich, C.; Clifton, S. W.; Schuster, L. N.; Chinwalla, A.; Delehaunty, K.; Dinkelacker, I.; Fulton, L.; Fulton, R.; Godfrey, J.; Minx, P.; Mitreva, M.; Roeseler, W.; Tian, H.; Witte, H.; Yang, S.-P.; Wilson, R. K. & Sommer, R. J. (2008), 'The Pristionchus pacificus genome provides a unique perspective on nematode lifestyle and parasitism.', Nat Genet 40(10), 1193--1198.

Hecht, J.; Stricker, S.; Wiecha, U.; Stiege, A.; Panopoulou, G.; Podsiadlowski, L.; Poustka, A. J.; Dieterich, C.; Ehrich, S.; Suvorova, J.; Mundlos, S. & Seitz, V. (2008), 'Evolution of a core gene network for skeletogenesis in chordates.', PLoS Genet 4(3), e1000025.

Rödelsperger, C. & Dieterich, C. (2008), 'Syntenator: Multiple gene order alignments with a gene-specific scoring function.', Algorithms Mol Biol 3, 14.

Dieterich, C. & Sommer, R. J. (2008), 'A Caenorhabditis motif compendium for studying transcriptional gene regulation.', BMC Genomics 9, 30.

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Integrative proteomics and metabolomics platform

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High throughput techniques are the tool for such large scale "-omics" studies allowing the obtainment of a complete picture of a determinate cell state, concerning its metabolites, transcripts and proteins. For example two-dimensional gas chromatography coupled to time-of-flight mass spectrometry (GCxGC-TOF-MS) is a promising technique to overcome limits of complex metabolome analysis using one dimensional GC-TOF-MS. However, single level study of a living organism (transcripts, proteins or metabolites) cannot give a complete understanding of the mechanism regulating biological functions. The integration of transcriptomics, proteomics and metabolomics data in the newly emerging field of System Biology, combined with existing knowledge, allows connecting biological processes which were treated as independent so far. In this context the aim of our group is to apply 'cutting edge' metabolomics and proteomics techniques for absolute quantification and analysis of turnover rates of proteins and metabolites; in addition, the further development of workflows for data analysis and integrative strategies will be in the focus of our interest.

Publications:

Christian N, May P, Kempa S, Handorf T, Ebenhöh O. (2009) An integrative approach towards completing genome-scale metabolic networks. Molecular BioSystems (in press) DOI:10.1039/B915913B

May P, Christian JO, Kempa S, Walther D. (2009) ChlamyCyc a new pathway tool for chlamydomonas reinhardtii. BMC Genomics 10: 209-212

Kempa S, Pietzke M, Strehmel N, Schwemmer T, Hummel J, Wienkoop S, Kopka J, Weckwerth W. (2009) An automated GCxGC-TOF-MS protocol for batch-wise extraction and alignment of mass isotopomer matrixes from differential 13C-labelling experiments: a case study for photoautotroph-mixotroph grown Chlamydomonas reinhardtii cells. JMB 49(1):82-91

Kempa S, May P, Wienkoop S, Usadel B, Christian N, Rupprecht J, Weiss J, Recuenco-Munoz L, Ebenhöh O, Weckwerth W, Walther D. (2008) Metabolomics- and Proteomics-Assisted Genome Annotation and Analysis of the Draft Metabolic Network of Chlamydomonas reinhardtii. Genetics 179: 1–10

Kempa S, Krasensky J, Dal Santo S, Kopka J and Jonak C. (2008) A central role of abscisic acid in stress regulated carbohydrate metabolism. Plos One 3(12):e3935

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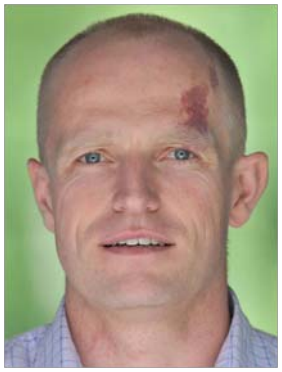
RNA Biology and Post-transcriptional Regulation



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Biological systems rely on the dynamic nature of gene expression to regulate cell survival, fate, homeostasis, to adapt to stress and to respond to environmental signals. A key aspect of the regulation of eukaryotic gene expression is the posttranscriptional control of mRNA stability and translation by microRNAs and RNA-binding proteins (RBPs).

We use biochemical and reverse genetic approaches in human and mouse cell systems to comprehensively map the mRNA-microRNA/RBPs interaction landscape with high resolution in order to investigate post-transcriptional regulatory networks.

Publications:

Hausser J*, Landthaler M*, Jaskiewicz L, Gaidatzis D, Zavolan M. Relative contribution of sequence and structure features to the mRNA-binding of Argonaute/miRNA complexes and the degradation of miRNA targets. Genome Res (in press)

Yi R, Pasolli HA, Landthaler M, Hafner M, Ojo T, Sheridan R, Sander C, O'Carroll D, Stoffel M, Tuschl T, Fuchs E. DGCR8-dependent microRNA biogenesis is essential for skin development. PNAS 2009;106:498-502.

Zhang Y, Landthaler M, Schlussman SD, Yuferov V, Ho A, Tuschl T, Kreek MJ. Mu opioid receptor knockdown in the substantia nigra/ventral tegmental area by synthetic small interfering RNA blocks the rewarding and locomotor effects of heroin. Neuroscience 2009;158:474-483

Landthaler M, Gaidatzis D, Rothballer A, Chen PY, Soll SJ, Dinic L, Ojo T, Hafner M, Zavolan M, Tuschl T. Molecular characterization of human Argonaute-containing ribonucleoprotein complexes and their bound target mRNAs. RNA 2008; 14:2580-2596

Landgraf P, Rusu M, Sheridan R, Sewer A, Iovino N, Aravin A, Pfeffer S, Rice A, Kamphorst AO, Landthaler M, et al. A mammalian microRNA expression atlas based on small RNA library sequencing. Cell 2007; 129:1401-1414.

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Systems Biology of Gene Regulatory Elements

The Rajewsky Lab uses computational and experimental methods to dissect, systems-wide, function and evolution of gene regulation in metazoans. One major focus is to understand more about gene regulation by small RNAs, in particular microRNAs. To probe general mechanisms in gene regulation of microRNAs, the lab works with cell lines. We are also investigating the function of small RNAs during very early development of C. elegans. Furthermore, the lab has established planaria as a model system within the lab. These freshwater flatworms are famous for their almost unlimited ability to regenerate any tissue via pluripotent, adult stem cells. The lab is studying the role of small RNAs in planarian regeneration.

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Publications:

Chen K; Maaskola J; Siegal ML; Rajewsky N. Reexamining microRNA site accessibility in Drosophila: a population genomics study. PLoS ONE 4 (5): e5681 (2009)

Stoeckius M; Maaskola J; Colombo T; Rahn HP; Friedlaender MR; Li N; Chen W; Piano F; Rajewsky N. Large-scale sorting of C. elegans embryos reveals the dynamics of small RNA expression. Nature Methods 6 (10): 745-751 (2009 -10)

Friedlaender MR; Adamidi C; Han T; Lebedeva S; Isenbarger TA; Hirst M; Marra M; Nusbaum C; Lee WL; Jenkin JC; Alvarado AS; Kim JK; Rajewsky N. High-resolution profiling and discovery of planarian small RNAs. Proceedings of the National Academy of Sciences of the United States of America 106 (28): 11546-11551 (2009-07-14)

Koralov SB; Muljo SA; Galler GR; Krek A; Chakraborty T; Kanellopoulou C; Jensen K; Cobb BS; Merkenschlager M; Rajewsky N; Rajewsky K. Dicer ablation affects antibody diversity and cell survival in the B lymphocyte lineage. Cell 132 (5): 860-874 (2008-03-07)

Ender C; Krek A; Friedlaender MR; Beitzinger M; Weinmann L; Chen W; Pfeffer S; Rajewsky N; Meister G. A human snoRNA with microRNA-like functions. Molecular Cell 32 (4): 519-528 (2008-11-21)

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Intracellular Signalling and Mass Spectrometry

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Cells receive many different stimuli from their environment that influence their metabolism, interaction with other cells, proliferation, survival and other cellular processes involved in homeostasis and health of the organism. The signals from different external stimuli are integrated by signal transduction cascades that involve a multitude of proteins. While we know a lot about the function of individual proteins there is little information about the system as a whole. One of the greatest challenges today is to explore signaling among all cellular proteins in parallel. Recent developments in mass spectrometry have dramatically improved the analytical power of this technology. We are using mass spectrometry -based quantitative proteomics to investigate intracellular signaling on a global scale.

Publications:

Moese S, Selbach M, Brinkmann V, Karlas A, Haimovich B, Backert S, Meyer TF. (2007) The Helicobacter pylori CagA protein disrupts matrix adhesion of gastric epithelial cells by dephosphorylation of vinculin. Cell Microbiol., 9, 1148-1161.

Selbach M, Mann M. (2006) Protein interaction screening by quantitative immunoprecipitation combined with knockdown (QUICK). Nature Methods,3, 981-983

Becker, D., Selbach, M., Rollenhagen, C., Ballmaier, M., Meyer, T.F., Mann, M. and Bumann, D. (2006) Robust Salmonella metabolism limits possibilities for new antimicrobials. Nature, 440, 303-307. (shared first authorship)

Backert, S., and Selbach, M. (2005) Tyrosine-phosphorylated bacterial effector proteins: the enemies within. Trends Microbiol., 13, 476-484.

Selbach, M., Moese, S., Hurwitz, R., Hauck, C.R., Meyer, T.F. and Backert, S. (2003) The Helicobacter pylori CagA protein induces cortactin dephosphorylation and actin rearrangement by c-Src inactivation. EMBO J., 22, 515-528.

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Mathematical Modelling of Cellular Processes

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Complex diseases are often characterised by an accumulation of multiple perturbations in rather large and complex cellular networks. The consequences of these perturbations, such as mutations or over-expression of proteins, can hardly be analysed by pure reasoning. Here, mathematical modelling contributes to a deeper understanding of the regulatory systems and provides thus a better basis for the interpretation of high-throughput data and identification of effective drug targets.

Our group develops and analyses mathematical models of signalling pathways and gene-regulatory networks in normal and disease states. For our investigations we use tools such as simulations, bifurcation analyses and sensitivity analyses. These give insights into the dynamical properties of the systems and help to identify most sensitive processes and critical regulations. Another important aspect is the investigation of cell specific differences in signalling and gene-regulatory networks since these are critically involved in the prediction of the efficiency and possible side-effects of drugs.

So far we use qualitative and quantitative dynamic modelling depending on the available experimental data. In the next future we also plan to apply logical modelling approaches which allow the description of large interaction maps with only minor knowledge about kinetic data (collaboration with Steffen Klamt, Magdeburg).

Publications:

J. Wolf, S. Dronov, F. Tobin & I. Goryanin (2007), The impact of the regulatory design on the response of EGFR-mediated signal transduction towards oncogenic mutations. FEBS Journal 274 (21), 5505-5517.

J. Wolf, S. Becker-Weimann & R. Heinrich (2005), Analysing the robustness of cellular rhythms, IEE Syst. Biol. 2(1), 35 -41.

S. Becker-Weimann, J. Wolf, H. Herzel & A. Kramer (2004), Modeling feedback loops of the mammalian circadian oscillator. Biophysical Journal 87, 3023-3034.

J. Wolf, H. Sohn, R. Heinrich & H. Kuriyama (2001), Mathematical analysis of a mechanism for autonomous metabolic oscillations in continuous culture of Saccharomyces cerevisiae. FEBS Letters 499, 230-234.

J. Wolf & R. Heinrich (2000), The effect of cellular interaction on glycolytic oscillations in yeast. A theoretical investigation. Biochemical Journal 345, 321-334.

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