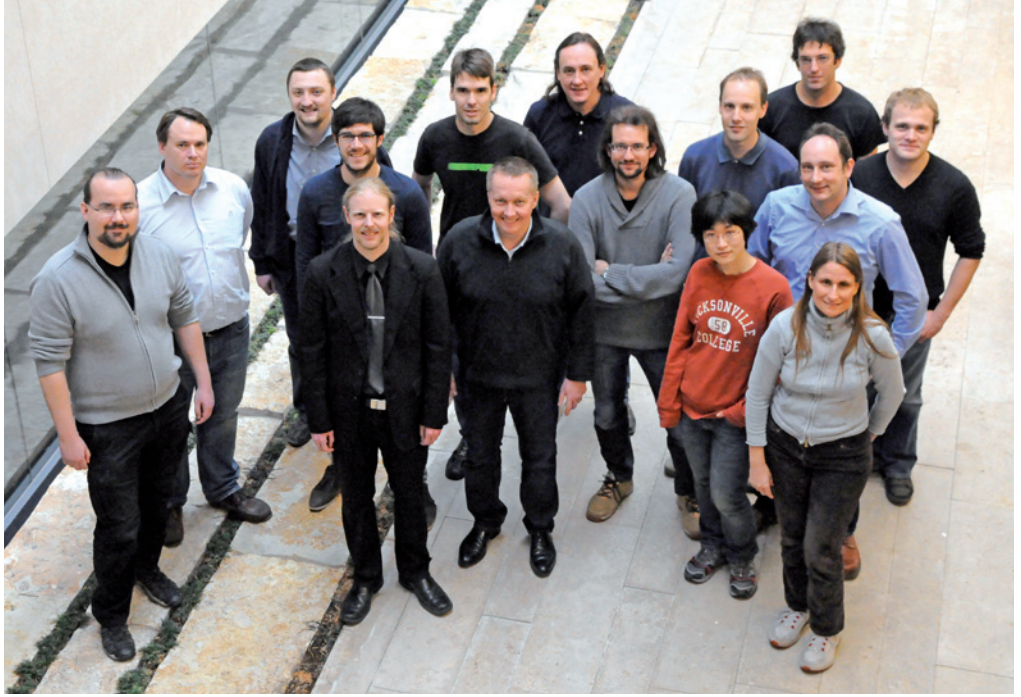


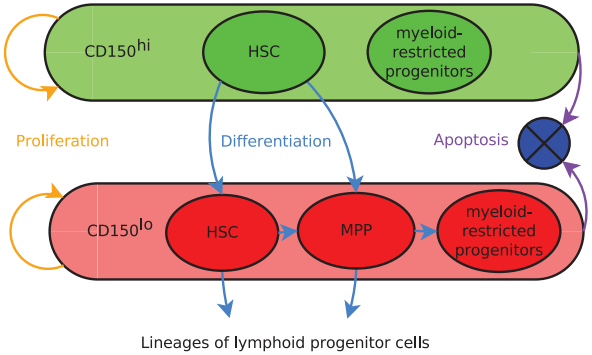
Core Facility Medical Systems Biology

Bioinformatics and Systems Biology

Head: Hans Armin Kestler

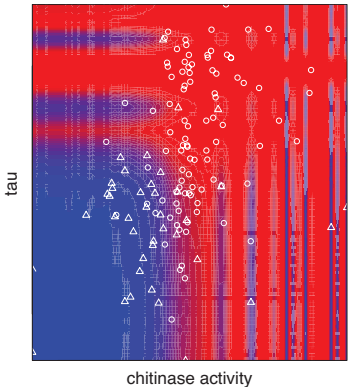
Biology and molecular medicine increasingly focus on the behavior of whole systems. Examples are metabolic, signal transduction or gene regulatory networks. Even small networks exhibit complex responses. Building models can aid the understanding of these systems and guide experiments to verify hypotheses. Modeling these networks mathematically requires the generation and formalization of knowledge on different levels, including the establishment of links between genes and cell status, and the characterization of co-regulated genes or associating gene changes to pathways or networks. The methods used for these investigations largely stem from the field of machine learning and statistics. Boolean networks are one type of model that can also be used to represent gene regulation. In this regard, we were recently able to find generalization error bounds that can be used for this type of model selection. Currently, we are investigating this topic further as it also has a strong impact on biomarker discovery with the aid of transductive algorithms (projects Florian Schmid, Ludwig Lausser). In these settings, feature selection and knowledge integration are paramount. To this end, we are also investigating the visualization and aggregation of knowledge from different platforms and across different species with regard to common denominators of stem cell aging (projects Sebastian Behrens, André Burkovski).

The Team:
Head of Core Facility: H. A. Kestler
Group Leader/Postdoc: M. Maucher, A. Groß, E. Sträng
PhD Students: J. Kraus, L. Lausser, M. Grieb, M. Müssel, A. Burkovski, S. Behrens, A. Fürstberger, G. Völkel, S. Wang, T. Schnattinger, F. Schmid
Students Study Programme Experimental Medicine: Computer Science
Additional Members of Thesis Advisory Committees: Kühl (Ulm), P. Frasconi (Florence), J. Hoheisel (Heidelberg), M. M. Comin (Padua), M. Buchholz (Marburg)



A model for irradiation-induced differentiation: A differentiation checkpoint limits hematopoietic stem cell self-renewal in response to DNA damage. Cell populations with defined expression levels of CD150 surface markers contain hematopoietic stem cells (HSCs) and myeloid-restricted progenitor cell subpopulations, populations with low CD150 levels additionally multi-potent progenitors (MPP). All cell types can undergo proliferation (orange arrows) or apoptosis (purple arrows). HSCs and MPPs may undergo differentiation (blue arrows).
Using a mathematical model based on delay-differential equations, we were able to show that differentiation across subpopulations of HSCs provides an explanation of the cell counts observed after irradiation.

Another aspect is how to arrive at these Boolean variables, i.e. how to binarize data from gene expression values in a well-defined way (project Markus Maucher). This is also directly linked to modeling signal transduction and gene regulation with Boolean functions either directly from literature and/or via reverse engineering or the direct inclusion of expert knowledge on known dynamics (projects Christoph Müssel, Melanie Grieb, Shuang Wang). Other approaches being investigated are models based on differential equations or probabilistic rules which usually require the inclusion of more global knowledge (projects Alexander Groß, Johann Kraus, Eric Sträng).
Other projects are concerned with sequence analysis and optimization algorithms (affiliated group members Axel Fürstberger, Thomas Schnattinger and Gunnar Völkel).



Biomarker discovery of Alzheimer's disease: Combination of the markers tau and chitinase activity enables estimation of decision regions to discriminate between Alzheimer's Disease (red) and no dementia (blue). Regions were estimated using a naive Bayes classifier on data from individuals with Alzheimer's Disease (circles) or no dementia (triangles). (Research Highlight: Nature Reviews Neurology 8, 178, 2012 and Watabe-Rudolph, M. et al. Neurology 78(8):569-77, 2012).

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Selected Publications:

- *Herrmann F, Groß A, Zhou D, Kestler HA*, Kühl M (2012): A Boolean Model of the Cardiac Gene Regulatory Network Determining First and Second Heart Field Identity. PLOS ONE, 7(10):e46798, *corresponding author*
- *Wang J, Sun Q, Morita Y, Jiang H, Groß A, Lechel A, Hildner K, Guachalla LM, Gompf A, Hartmann D, Schambach A, Wuestefeld T, Dauch D, Schrezenmeier H, Hofmann W, Nakauchi H, Ju Z, Kestler HA, Zender L, Rudolph KL (2012): A Differentiation Checkpoint Limits Hematopoietic Stem Cell Self-Renewal in Response to DNA Damage. Cell, 148(5):1001–1014.*
- *Hopfensitz M, Müssel C, Wawra C, Maucher M, Kühl M, Neumann H, Kestler HA: Multiscale binarization of gene expression data for reconstructing Boolean networks (2012): IEEE/ACM Transactions on Computational Biology and Bioinformatics, 9(2):487–498.*
- *Maucher M, Kracher B, Kühl M, Kestler HA (2011): Inferring Boolean network structure via correlation. Bioinformatics, 27(11):1529–36.*
- *Meyer LH*, Eckhoff SM*, Queudeville M, Kraus JM, Giordan M, Stursberg J, Zangrando A, Vendramini E, Moericke A, Zimmermann M, Schrauder A, Lahr G, Holzmann K, Schrappe M, Basso G, Stahnke K*, Kestler HA*, te Kronnie G*, Debatin KM (2011): Early Relapse in Pediatric ALL is identified by Time To Leukemia in NOD/SCID mice and is characterized by a gene signature in- volving survival pathways. Cancer Cell, 19(2):206-17. * equal contribution*
- *Kraus JM, Kestler HA (2010): A highly efficient multicore algorithm for clustering extremely large datasets. BMC Bioinformatics, 11(1):169.*