

Healthcare industry BW

Hans Kestler brings order to biological data

Hans Kestler works on the borders between the faculties, administration and different disciplines at Ulm University. Molecular biologists and life scientists at Ulm University fight over the lively engineer who is in his late forties. They all need the assistance of the systems biologist who knows how to deal with the enormous amounts of data they produce using mathematical models and algorithms.

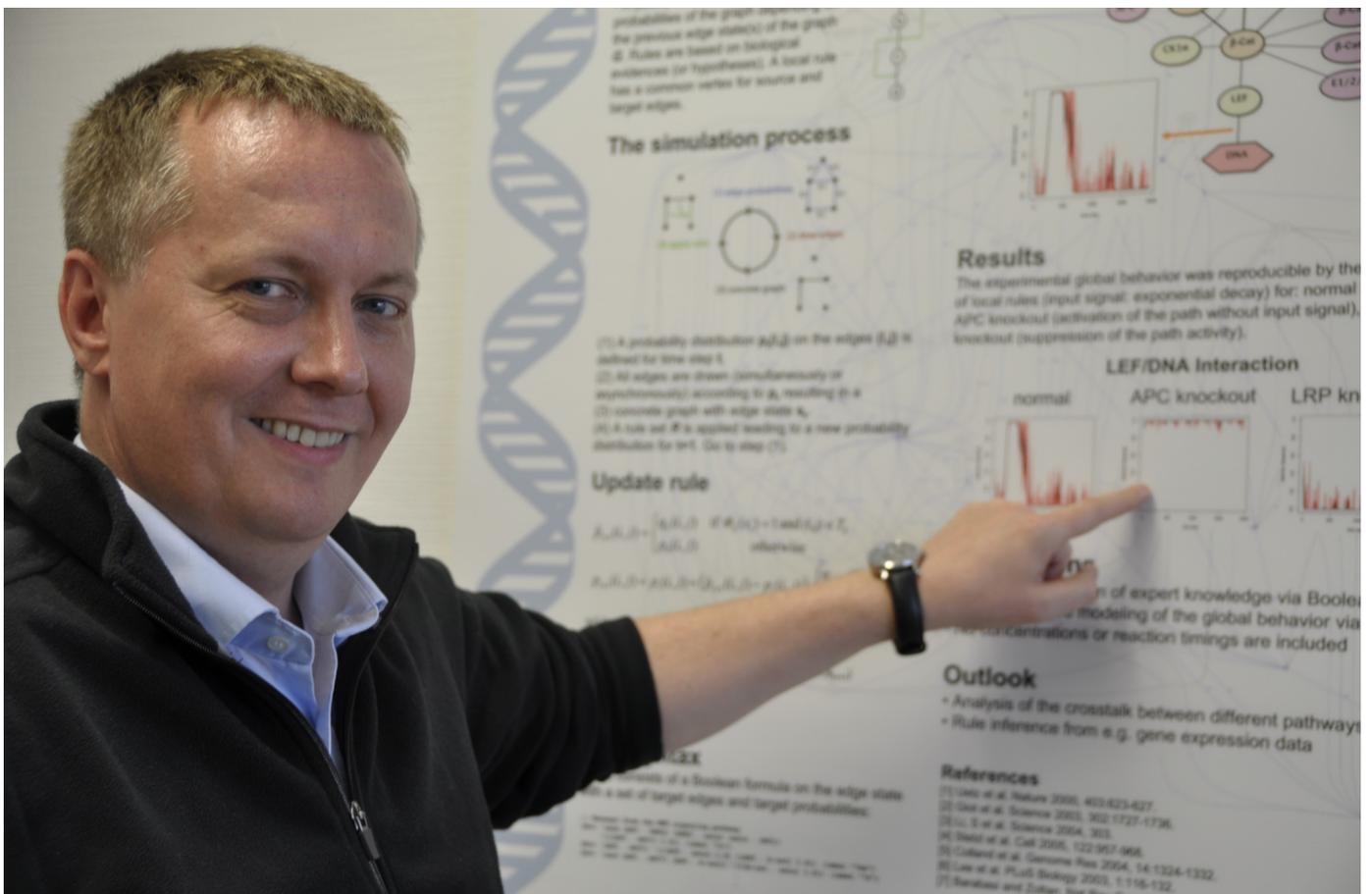
Kestler is an electrical engineer ("this is applied mathematics" he says) who heads up the Bioinformatics and Systems Biology research group at the Institute of Neuroinformatics at the University of Ulm. He is unable to say exactly how many research projects he is involved in, as there are far too many. "I'm drowning in work," he says casually. Kestler has co-authored an immense number of life sciences papers written by Ulm University researchers. Asked whether he is worried about this heavy workload he simply replies: "I love plenty of action."

Machine learning methods are required for analysing the large amount of data

Two paradigm shifts in biology have made people such as Kestler essential for life scientists: high-throughput methods, -omics technologies and molecular imaging have led to a huge increase in scientific data. "We need statistical machine learning methods to be able to cope with the data and generate knowledge from them," Kestler says. He calls this process "knowledge extraction" on a symbolic level: measurement data at a stage when they still have no meaning need to be transferred to a knowledge representation level, using, for example, the "if-then" rules.

The second paradigm change has vastly increased the complexity of knowledge of cellular mechanisms. Ten years ago, signalling cascades were regarded as isolated units within the cell rather than as a mesh of interconnected networks with important connections that enable crosstalks between pathways. Gone are the days when individual researchers were able to play through all possible configurations in a single experiment. This is now done by powerful computers that are given instructions by bioinformaticians like Hans Kestler.

An iterative process that requires close cooperation



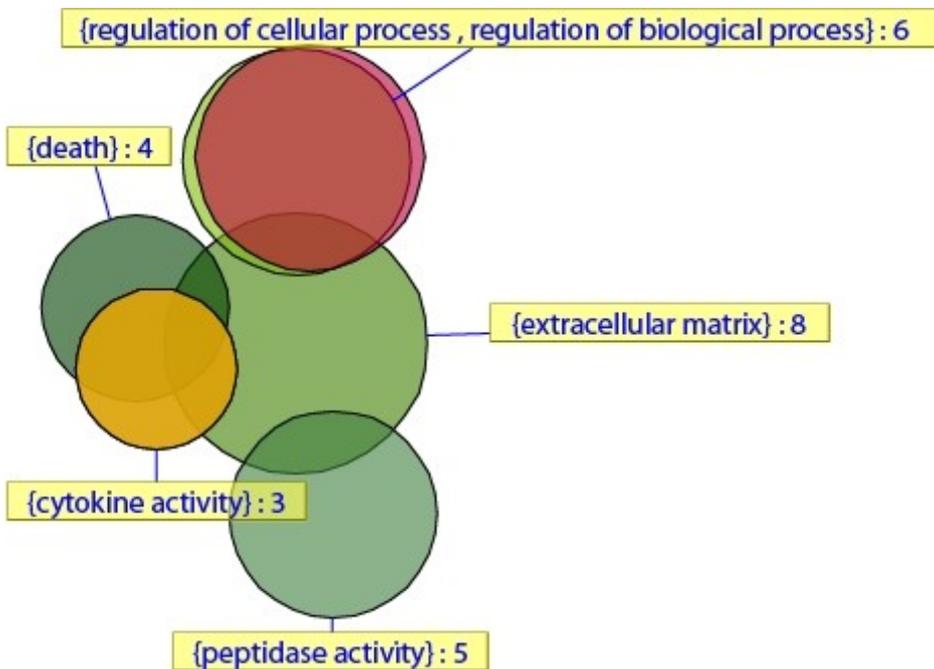
PD Dr. Hans Kestler
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Hans Kestler uses machine learning, statistics and dynamic modelling (differential equation systems and simplifications such as Boolean networks) methods to attempt to manage the huge amounts of data. This requires biologists and mathematicians to work closely together. Kestler refers to the need to test an in silico model against laboratory data and all available knowledge as an iterative process; a process that needs to be adapted and optimised based on falsification, verification and improvement. Kestler believes that a relatively small campus like Ulm University is perfect for such close collaboration.

He has been working at Ulm University since 1992. After finishing his studies, he decided against a job in industry and instead accepted the offer of a post at Ulm University Hospital. The Department of Cardiology was looking for an expert who could classify highly amplified electrocardiograms using neural networks. This enabled Kestler to continue working on the topic that he had studied for his degree thesis. He accepted the offer on the condition that he could do his doctorate in the Faculty of Computer Sciences. "Being an electrical engineer, I was basically an alien in the informatics faculty," said Kestler explaining that this required him to go through a three-hour examination by three professors. After three-and-a-half years in the Department of Cardiology, Kestler continued his doctorate in the Department of Neuroinformatics headed up by Günther Palm, but kept his room in the Department of Cardiology. Kestler has been active in the two disciplines ever since.

Research lectureship as the starting point for his subsequent activities

In 2003, Kestler was awarded a five-year research lectureship by the German Stifterverband. The lectureship did not really fit into any defined slot, but was so successful that another foundation



The Venn diagramme is used to visualise complex relationships between genes.
 © Kestler, Uni Ulm

injected additional money. The lectureship gave his research a decisive boost. His supervisor Guido Adler, one of the most influential university medical professors and now director of the Heidelberg University Hospital, also played a major role in that he was responsible for making Kestler 100% interested in the field of bioinformatics.

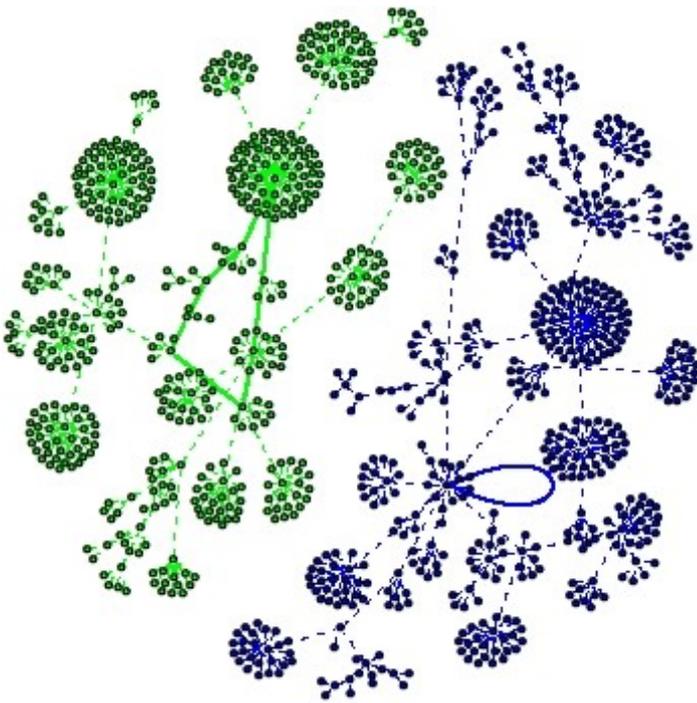
The research lectureship got Hans Kestler known at Ulm University relatively quickly, resulting in numerous cooperative projects. In 2005, he became part of a group of researchers led by Thomas Gress (Internal Medicine II) and he developed a new method for visualising complex gene relations using a Venn diagram which shows all possible logical relations between a finite collection of sets, in this case genes. This provides information on existing relations and enables the researchers to deduce information on others.

The reason why developmental biologists need models

Kestler also quickly came into contact with evolutionary biologist Michael Kühl (Director of the Institute of Biochemistry and Molecular Biology) who was looking for somebody who would be able to assist in the modelling of dynamic biological systems. Kühl had discovered that the interspecific differentiation of the heart is regulated by a highly conserved gene network but needed mathematical methods to explore whether the gene network adapts to species and whether it expands or potentially interacts with other signalling networks.

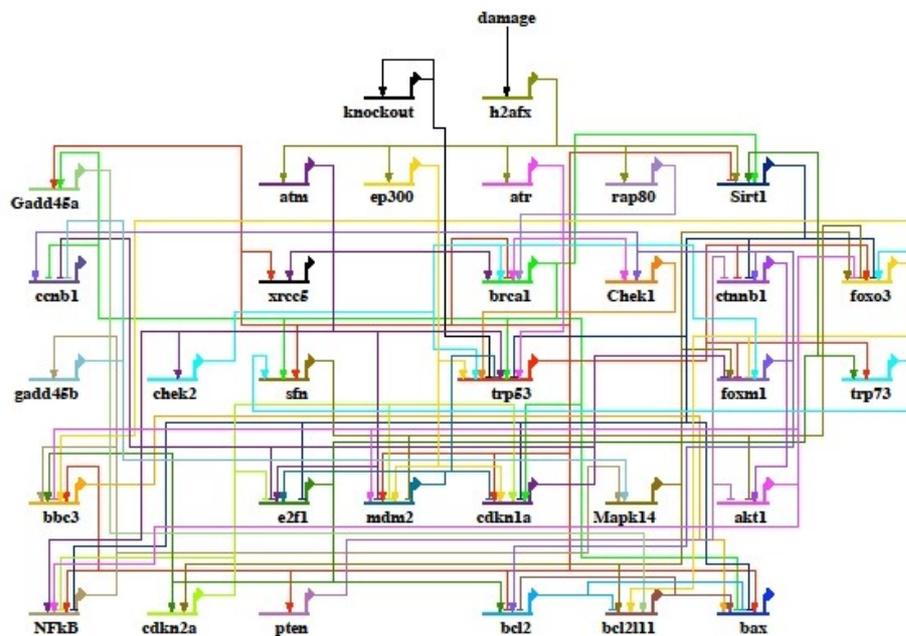
“We were glad to finally have an issue to which our learning systems would make a relevant contribution,” says Kestler referring to the work he did back at that time. He is enthusiastic about the “extremely short distances here in Ulm” where it only takes him a few minutes to get from one department to another, to meet a life sciences colleague in the cafeteria or to see Michael Kühl in order to exchange information about the mathematical model of the WNT signalling pathway which plays a crucial role in the development of cancer, embryonic development and in ageing.

Mathematical models for investigating molecular ageing



A state diagram provides information about the behaviour of a biological system, for example, or can be used to determine the reliable use of a particular interface of a system.

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Graphical representation of the consequences of a mutation in the h2afx gene which is involved in nucleosome formation and hence contributes to the organisation of DNA.

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The highlight of his research activities at Ulm University to date is “Systar” (Systems biology analysis of impaired stem cell function and regeneration during ageing), for which he and Lenhard Rudolph (now at the Leibniz Institute of Ageing Research) have landed a big fish. The German Federal Ministry of Education and Research (BMBF) has awarded the researchers 7.4 million euros for the cooperative project. The project commenced in late 2012 and brings together 14 research groups – clinicians, basic researchers, bioinformaticians and mathematicians – from Ulm University with the aim of identifying the molecular mechanisms that are associated with age-dependent reduced stem cell function and the loss of regenerative ability. One of the researchers’ major goals is to use systems biology approaches for generating mathematical models of stem cell ageing on the basis of experimental data. Kestler’s research group carries out and improves the analysis of the complex data obtained in another large-scale project, the SFB 1074 entitled ‘Experimental Models and Clinical Translation in Leukaemia’ in Ulm which aims to transfer basic cancer research to clinical applications. The analyses done as part of this project enable robust predictions to be made on the classification of high-dimensional data of low sample size. Kestler’s expertise is in great demand in many life sciences research areas: he is working with pathologists to establish a lymphoma database and also with virologist Thomas Mertens on a database that contains information about the drug resistance of certain HCM (human cytomegalovirus) genome mutations. A paper recently published in a reputable journal (Watabe-Rudolph, *Neurology*, 2012) on a potential Alzheimer’s disease biomarker also shows how indispensable bioinformatics has become for life sciences researchers.

Unsolved problem: the use of research data

It has barely become general knowledge that life scientists now depend on the assistance of mathematicians/informaticians in their effort to elucidate the large amounts of data they produce and are hence also dependent on immense, rapid computer capacities, when a new problem has already arisen. At a recent workshop run by the German Research Foundation (DFG), Kestler pointed out that the use of research data, their long-term storage and personnel-intensive management is a new problem that needs to be solved.

It is no great surprise that Hans Kestler’s staff (biotechnologists, physicists, computer scientists) are in virtually every department on the Ulm University campus and that they are funded by different institutions and different funding pots. “It’s all a bit heterogeneous, but it all fits together,” says Kestler with a smile. This links in with Kestler’s announcement that he and Martin Bossert from the Institute of Communications Technology are about to submit a proposal to the DFG’s InKoMBio (Information and Communication Theory in Molecular Biology) priority programme which provides funds for interdisciplinary projects between information and communication scientists on the one hand, and biologists and medical scientists on the other. There seem to be hardly any disciplines that can do without applied mathematics now.

Publication:

Watabe-Rudolph M et al.: Chitinase enzyme activity in CSF is a powerful biomarker of Alzheimer disease, *Neurology*. 2012 Feb 21;78(8):569-77. (doi: 10.1212/WNL.0b013e318247caa1. Epub 2012 Feb 8.)

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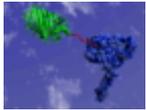
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