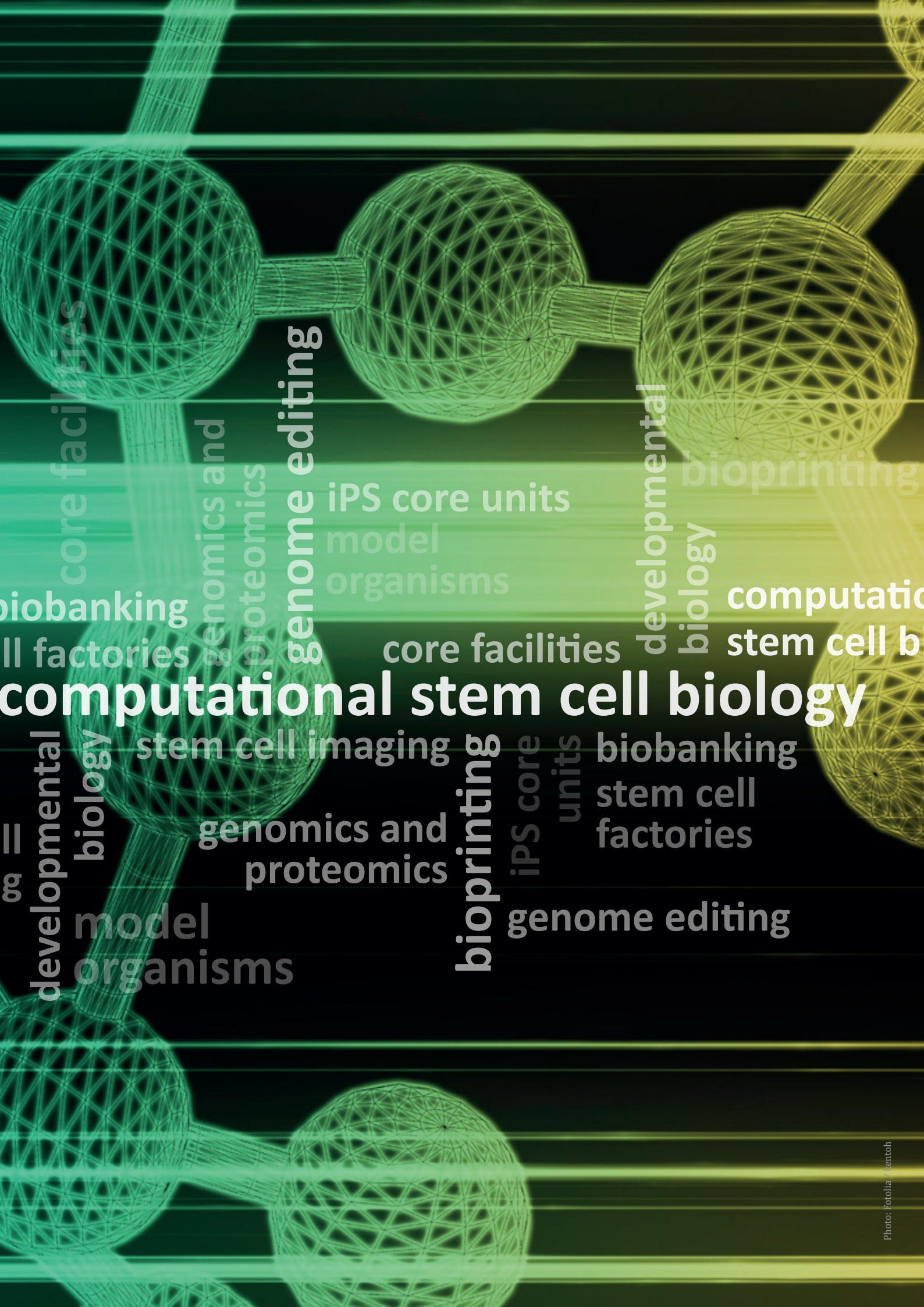

Photo: Fotolia / kentoh

Bioinformatics analysis

Navigating a sea of digital data

High-throughput molecular technologies and high-definition imaging are generating enormous amounts of data in stem cell biology. This large volume of data cannot be handled without computer support. Big data not only has great potential, it can also cause problems. Systems biologists and bioinformatics scientists are trying to use mathematical models to extract some insights from the mountains of data. To be able to predict stem cell characteristics, it is essential to look at important details as well as at the big picture.

High-throughput molecular analyses, so-called omics technologies, and digital imaging techniques have significantly altered biomedical research and are opening up entirely new insights into vital functions. But they are also generating enormous amounts of data, of which only a fraction can currently be analyzed. This is referred to as the "big data problem", since the growing amount of data does not automatically mean that greater insights are obtained.

Stem cell researchers also face the challenge of extracting the information that is relevant to their topics from the mountains of digital data before they can analyze it. Then there is the next step of making the data and the findings derived from that data available to the scientific community through suitable networks.

Differing approaches

Ingo Röder of the Institute for Medical Informatics and Biometry (IMB) at TU Dresden has been working for years on the mathematical modeling of stem cell systems. Using computer simulations and statistical methods, he is getting closer to understanding complex phenomena like the pluripotency of embryonic stem cells (ES cells).

Photo: TU Dresden / Ingo Röder

Computer-based analysis of biological data

Researchers from around the world have now compiled an enormous amount of molecular data on this topic. For the analysis, two approaches to developing computer-based models dominate. "Some researchers are looking at huge, overarching regulation networks, while the others are limiting themselves to analyzing smaller partial systems," says Ingo Röder. There is good rationale for both approaches, he says. While the approach driven by large amounts of data tries to identify complex relationships, it often does not move beyond the descriptive level. "Biological regulation networks are extremely complex and therefore very difficult to describe quantitatively in their entirety." With their mathematical description, they are currently asking primarily "What?" questions. "This provides an important overview of regulatory structures but in many cases does not provide mechanistic explanations," says Röder.

Max Planck Institute for Molecular Genetics

MPIMG

MPIMG

Research at the Max Planck Institute for Molecular Genetics (MPIMG) concentrates on genome analysis of man and other organisms to contribute to a global understanding of many biological processes in the organism, and to elucidate the mechanism behind many human diseases.

It is the overall goal of all MPIMG's groups to gain new insights into the development of diseases on a molecular level, thus contributing to the development of cause-related new medical treatments. In this context, stem cell research is gaining increasing importance. In particular, MPIMG researchers are working on a better understanding of gene regulation networks for tissue formation and homeostasis, as their dysfunction may result in numerous diseases

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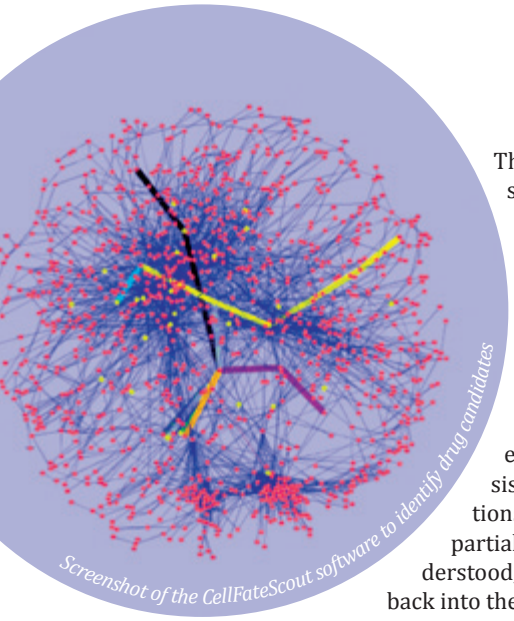


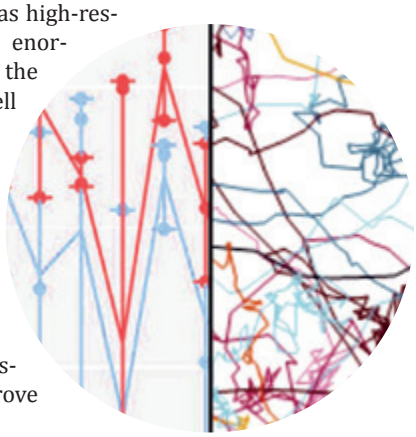
Screenshot of the CellFateScout software to identify drug candidates

The approach of only considering portions of a biological system is quite different. Here, the question of "Why?" is foregrounded. "Using such models, it becomes easier to really understand underlying mechanisms, and to then check them experimentally on the basis of specific model predictions," explains Röder. Once partial systems have been understood, he says, they can be fitted back into the larger puzzle.

Looking at single cells

Modern technologies help make it possible to look at details. Single-cell analysis has become an important source of data for systems biologists and mathematical modelers. Even cells within defined cell populations, like stem cells or differentiated cells, are often not homogeneous, as they differ from one another in terms of their specific properties. A precise view of individual cells is important for recognizing heterogeneities and their influence on the organization of the system.

Single-cell analysis can, for example, be used to analyze all RNA molecules and thus gene activity in a single cell. But it is not only molecular data that can be recorded. "We are also looking at the behavior of cells, at their communication with neighboring cells, and at the influence of spatial structures," says Röder. Such functional single-cell analyses, using techniques such as high-resolution imaging, produce enormous amounts of data. In the area of theoretical stem cell biology, the Dresden-based researchers are joined in evaluating single-cell analyses by Fabian Theis and his colleagues at Helmholtz Zentrum München. The scientists have developed statistical methods that make it possible to simplify and improve analysis.



Photos: IBIMA Rostock / Georg Fülle, TU Dresden / Ingo Röder

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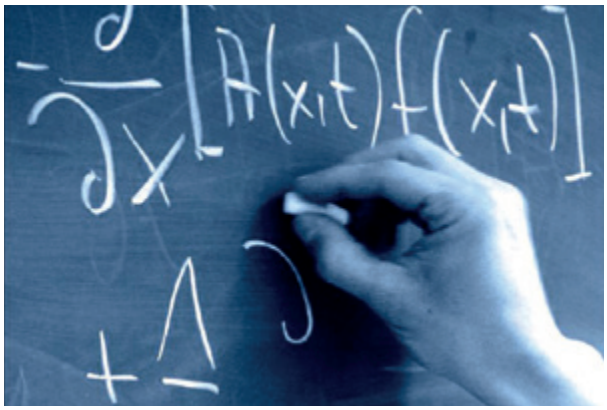


Photo: TU Dresden / Ingo Röder

Setting up new facilities

In Germany, researchers are still in the early stages of working with big data and setting up the appropriate facilities. The Federal Ministry of Education and Research (BMBF) is currently funding the development of two competence centers for Big Data. The Berlin Big Data Center (BBDC) is being set up under the direction of TU Berlin, and the Competence Center for Scalable Data Services and Solutions (ScaDS) is emerging under the direction of TU Dresden and Leipzig University. Röder reports that ScaDS will focus on informatics-based strategies for dealing with huge amounts of data from the life sciences. In addition to setting up efficient data structures, this also involves questions such as: How can specific knowledge be extracted from the data? How do we deal with changing data?

In the future, stem cell researchers could also benefit from the German Network for Bioinformatics Infrastructure (de.NBI), for which the BMBF is likewise providing €22 million in funding. This virtual association will seek to improve and sustainably secure the availability of both hardware and bioinformatics tools in the life sciences. Six research centers have been selected: the DKFZ in Heidelberg, the universities in Bochum, Tübingen and Freiburg, the Leibniz Institute of Plant Genetics and Crop Plant Research (IPK) in Gatersleben, and Bielefeld University, which is coordinating the efforts. The group will begin work in March 2015.

To date, Röder has observed a very pragmatic approach to working with Big Data, one that focuses primarily on storing the large amounts of data rather than on creating value creation or managing the life cycle of data. "In this regard, we are still beginners," he observes. *Text: Philipp Graf*

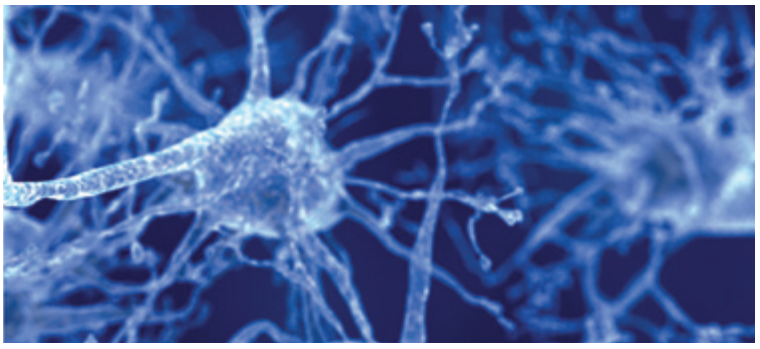
Modeling neurodegenerative disease

life technologies™

"Eureka, it worked!!!!". Albert, in an ecstatic state, ran into his boss's office nearly smashing the door against his desk. "You were right, your idea worked beautifully. I could differentiate the iPSCs into neuronal stem cells quickly and easily. Better still, I was able to derive various neuronal subtypes from different brain regions, such as **GABAergic,- dopaminergic-** and **motor-neurons,** from these neuronal stem cells! Take a look!" There was a slight tremble in Albert's voice as he contemplated a possible Nature paper, the Nobel Prize or, even better, a pat on the back from his boss!

"And guess what – I got this job done so quickly, it was even faster than baking a cake…. at least faster than if I'm baking it…" With a broad smile on his face he reflected on the past few days work in his lab from reprogramming **fibroblasts** into iPSCs in only 14 days using the new **CytoTune®-iPS 2.0 Sendai Reprogramming Kit,** to culturing isolated iPSC colonies under feeder-free conditions using **Essential 8™ Medium,** and characterizing colonies for pluripotency and differentiation potential using the **TaqMan® hPSC Scorecard™ Assay.** This had actually been Albert's first step into the wonderful world of qPCR, which he hadn't trusted himself with in earlier times. He admitted that he didn't really understand qPCR, but who cares – with ScoreCard™ and the cloud-based data analysis software he could get much more out of the **beige-blue boxes** than in the past. He could now also proudly add the first meaningful qPCR data to his lab notebook.

Using the **Gibco® PSC Neural induction Medium** he was able to quickly and easily differentiate his iPSCs into a population of NSCs, and all without having to undergo the tedious process of generating embryoid bodies or picking neural rosettes which the lab seemed to have been doing for what felt like 250 years! "This stuff is like packet soup" – he told his wife one evening when he came home from the lab. "Just add it to your iPSCs, wait 7 days and, voilà you have your population of NSCs." "And you wont believe



the efficiency!" He had never dreamt that there could be such a simple method to achieve a 20-fold expansion in final NSC count from the iPSC starting material he had added to the Neural Induction Medium just 7 days prior. With so much material available he could even afford to differentiate his NSCs towards, not just one, but three different neuronal cell types, **GABAergic,- dopaminergic-** and **motor-neurons** in parallel. Albert had already spent quite enough time developing a medium to induce NSC differentiation from iPSCs. So now, following a thorough search of the literature, he decided to use conventional protocols to differentiate his NSCs towards the desired neuronal-subtype for his research work. Admittedly this took him some time, but in the end he succeeded and his wife, his boss and also Albert himself were happy at the outcome. His boss, because once again his ideas and concept had come to fruition, Albert, because he could go home in the evening at a reasonable hour, and his wife, because Albert took her out for dinner – to the fish and chip shop on the corner of their street…

Please visit lifetechnologies.com/stemcells to receive more information.