Computational stem cell biology

Lending predictability
to stem cells

The field of experimental stem cell research is producing a flood of data that would be impossible to manage without computational support. This discipline of bioinformatics for the analysis and organization of biological data is one of many related fields that are indispensable for modern stem cell research. Systems biologists are using mathematical models and computer simulations to delve deeper than ever before into the fascinating properties of stem cells. A growing number of specialists in Germany are dedicating themselves to the computational view of stem cells, and are in the process of changing the face of clinical research.

Understanding the behavior of – and lending an element of predictability – to stem cells: this is the objective of a growing body of systems biologists, mathematicians and computer scientists active in the field in Germany. The possibilities for the computer-based analysis of experimental data have improved significantly in the past ten years. "We now have the modern technologies needed to collect a sufficient amount of quality data. These give us the experimental basis to test our stem cell models," says Ingo Röder from the Institute for Medical Informatics and Biometry (IMB) at the Technical University of Dresden. In the mathematician's opinion, there is a growing acceptance among his colleagues to also bring the 'theorists' on board in the planning of studies. Molecular biologists and physicians are recognizing that theoretical approaches can provide impetus not only for fundamental insights but also for eventual clinical application. At the same time, it is clear that the avalanche of data produced by molecular biology laboratories, such as from high-throughput analyses, can only be properly managed with the help of serious computing power and methods of bioinformatics.

The dynamic cell

Together with Rostock-based bioinformatician Georg Fuellen, Ingo Röder is one of the initiators of the GSCN working group 'Computational methods stem cell biology.' Röder's working group has been engaged for some years with the mathematical modeling of stem cell systems. His team is focusing on the adult stem cells of the blood-forming system – the hematopoietic stem cells (HSCs). In particular, the researchers are hoping to understand how HSCs alternate between different cellular states. In recent years, they have built up a clear picture of the dynamic decision-making processes that take place during the transition to different cell states, namely a flexible switching back and forth between molecular states. "Very early on, we predicted from our mathematical models that two states exist in HSCs: dormant and ac-

tive cells, which can divide and multiply," explains Röder. Physicians and stem cell biologists have now experimentally confirmed these predictions. "These data help us to further develop existing models and to sharpen our hypotheses," says Röder. In the case of a blood cancer disease, his team has already demonstrated how a theoretical HSC model can be transferred to clinical practice: an important role in Chronic Myeloid Leukemia (CML) is played by 'dormant' stem cells, which are unaffected by treatment. There is thus a hypothesis that these dormant cancer stem cells could be reactivated and, in combination with other substances, attacked more effectively through treatment with cell cycle-stimulating agents such as IFN-α. This would not only increase the effectiveness of a therapy but would also reduce the risk of the recurrence of the disease following a successful treatment. "With our computer program, we can run through the possibilities of such a therapy in a range of different conditions." Röder is certain that in the medium term, such calculations will be decisive in improving the design of clinical trials. Real world examples already exist for how patients can benefit from the findings of the Dresden stem cell mathematician, for example predictions about different drug dosages and the duration of a specific therapy. "In collaboration with clinicians in Mannheim and Jena, we have already successfully used our models to predict the clinical course of a CML treatment with the drug Imatinib." This also allows prognoses to be made on the optimal time for a patient to end a course of therapy.

German stem cell modelers

In Dresden, Ingmar Glauche has put together a junior group for systems biology that is likewise occupied with these and related issues of HSCs. Other dedicated stem cell modelers are also at work at the University of Leipzig. There, the head of the Institute for Medical Informatics, Statistics and Epidemiology, Markus Löffler, together with Jörg Galle, group leader at the Interdisciplinary Center for Bioinformatics, specializes in simulations and models of the behavior of intestinal stem cells in tissue niches, i.e. the microenvironment in which they are embedded. Stem cell phenomena is a priority research area for the team headed by Fabian Theis, Chair of Computational Modeling in Biology at the TU Munich. Here, the mathematician Theis is working on single-cell analysis, which is also highly relevant for stem cell biologists. Such technologies for the analysis of individual cells are becoming progressively more sophisticated but remain extremely laborious. Moreover, the specific handling of cells can be the cause of significant measurement inaccuracies. The consequence of this is random statistical noise in analysis, which can swamp the sought-after fine
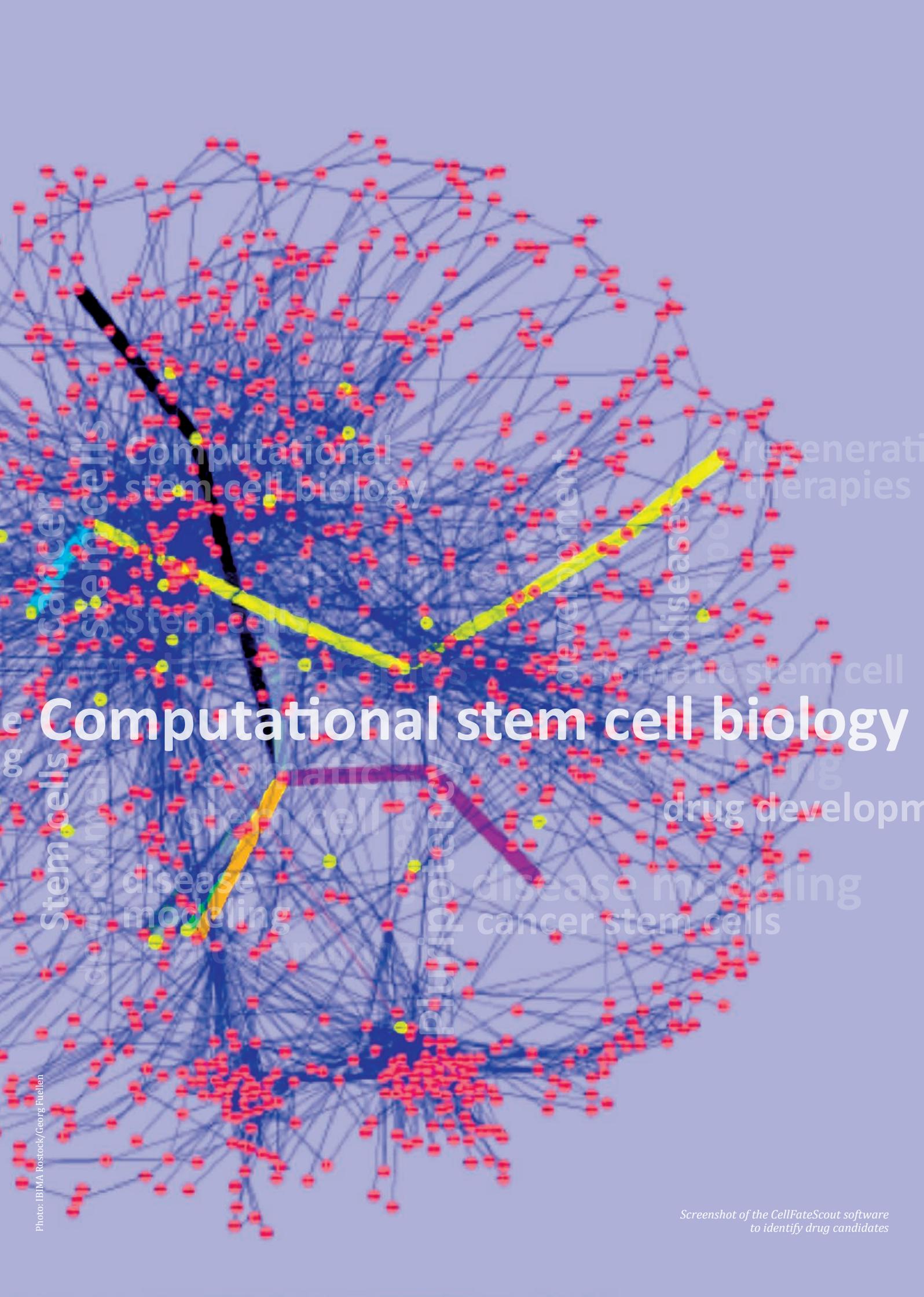
Computational stem cell biology

Screenshot of the CellFateScout software to identify drug candidates
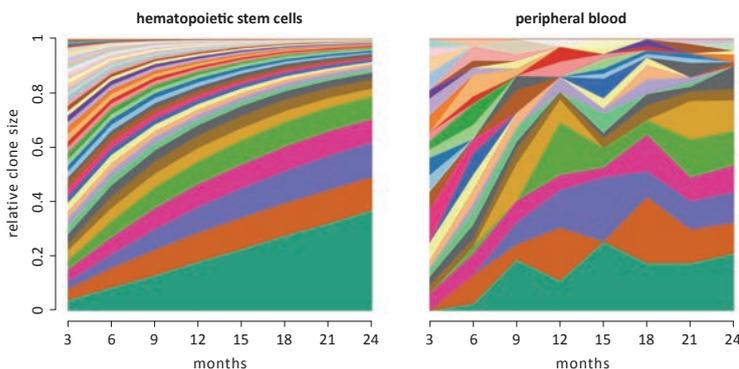
Simulation of a clonal dynamic of hematopoietic stem cells and cells in the peripheral blood

distinctions in the data, for example information relating to gene regulation. One solution under consideration by Theis and his team is the study of larger samples, each of ten cells. Aided by statistical methods, this enables the calculation of significantly more accurate results – an outcome already proven in experimental studies. Researchers in Berlin, Freiburg, Plön, Heidelberg and Aachen are likewise – though not exclusively – occupied with mathematical models for stem cell biology.

Digital magnifier for pluripotency

The stem cell development program is influenced by a complex interplay of transcription factors, signaling molecules and epigenetic mechanisms. The high-throughput analyses that aim to shed light on these aspects are producing vast quantities of data. These data, which originate in particular from genome-, transcriptome- and proteome analyses, must be evaluated, integrated and interpreted. So what connects the various regulatory components in stem cells? And what are the relationships between them? These questions require the know-how of bioinformatics. Today, numerous locations across Germany are specialized in the data analysis of the molecular processes in stem cells. Together with his team, Georg Fuellen, head of the Institute for Biostatistics & Informatics in Medicine & Ageing Research,

has developed the 'PluriNetWork' database and the software 'ExprEssence'. These tools enable the even closer scrutiny of interactions between hundreds of genes and proteins, such as in the induction of pluripotency or during the first steps of cell differentiation. Once more is known about them, the processes can be chemically influenced. It is anticipated that the innovative methods of bioinformatics will markedly improve the search for suitable drug candidates. With the assistance of corresponding algorithms, it is also possible to analyze combinations of drug candidates for their effects. The research work being carried out by Marcos Araúzo-Bravo at the Max Planck Institute for Molecular Biomedicine in Münster is aimed at deciphering the complex ensemble of transcription factors and their target structures in stem cells. Araúzo-Bravo's team has developed algorithms for the analysis of the epigenetic fingerprint of pluripotent stem cells. At the Max Delbrück Center in Berlin-Buch, Miguel Andrade's working group is specialized in data analyses of the stem cell system. At the Max Planck Institute for Molecular Genetics in Berlin, Martin Vingron's team also aims at the elucidation of pluripotency with bioinformatical approaches. Bioinformatics methods for the analysis of stem cells are also being developed by researchers at research institutions in Aachen, Cologne, Munich and Saarbrücken.

"Our GSCN working group aims to raise awareness of the value of theoretical models for biological questions. We want to more strongly introduce our ideas into the community," says Ingo Röder, who sees the working group as a possible point of contact for stem cell biologists, both to exchange ideas and to launch bilateral projects. All of which is intended to bring us ever closer to the fascinating properties of stem cells.

Text: Philipp Graf

Graphics: IMB, TU Dresden / Ingmar Glauche

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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