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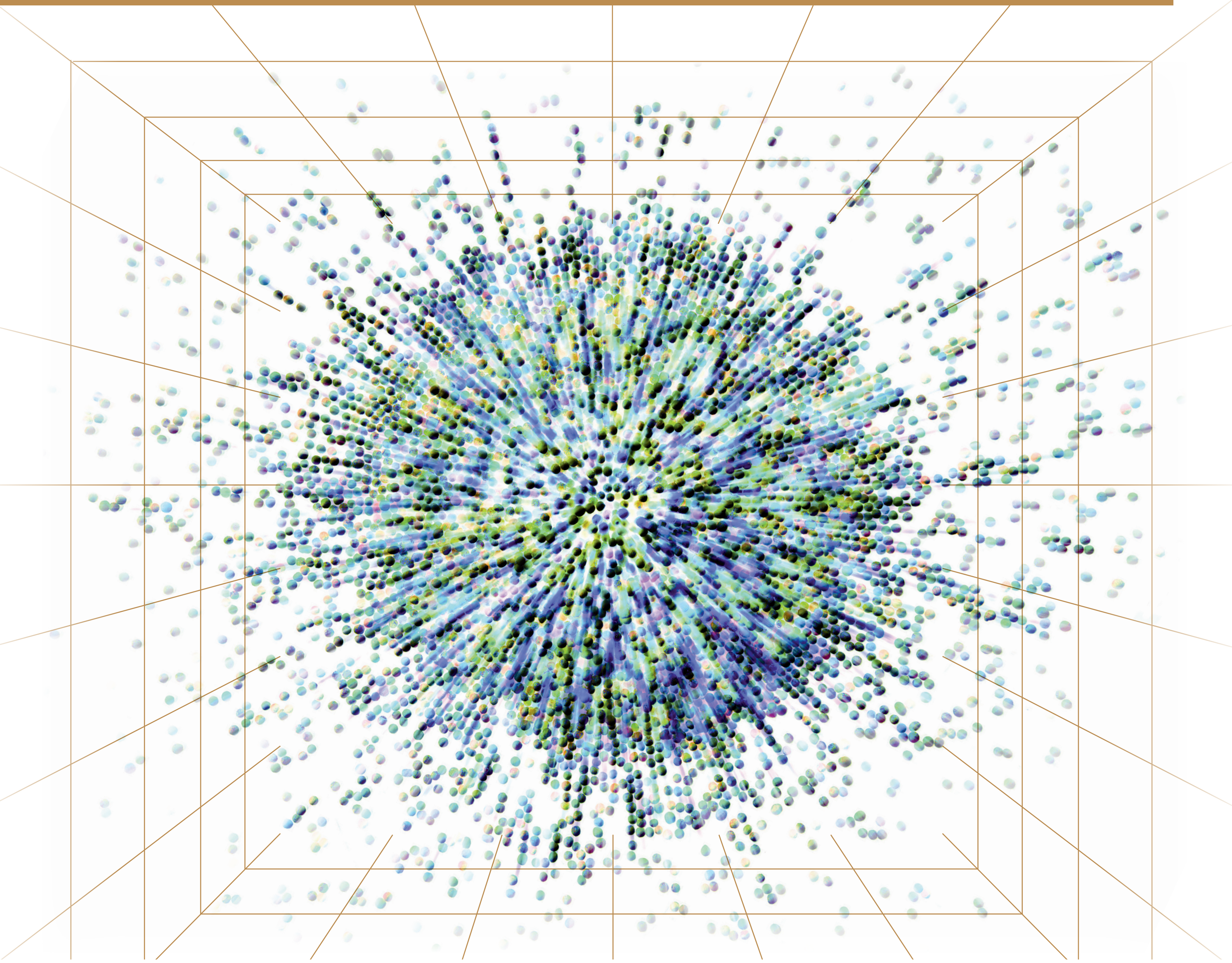
Report on Tomorrow's Science



Life sciences in transition

Challenges of omics technologies for Germany's infrastructures in research and teaching

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Report on Tomorrow’s Science

Life sciences in transition

Challenges of omics technologies for Germany’s infrastructures in research and teaching

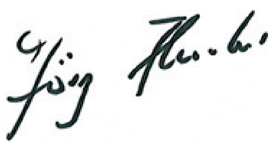
Preface

One of the main tasks of the German National Academy of Sciences Leopoldina is to provide science-based advice for policymakers and society. This includes topically systemic potentials and challenges of science development in Germany. The new publication series *Report on Tomorrow's Science* addresses issues of science development in Germany, which are particularly relevant in the medium and long term to the relationship between science, policy and society. This relates, for example, to research infrastructures, training young scientists or knowledge transfer.

Leopoldina's first *Report on Tomorrow's Science* is dedicated to *Life sciences in transition*. As in other areas of science, life sciences are now also changing as a result of new technologies being used. By using bioanalytical high-throughput methods large quantities of data about life processes can be obtained in a short period of time with the aim of understanding these processes to a higher level of precision. It is hoped to gain, for example, wide-ranging findings on the causes of illnesses and based on that the development of targeted therapies, new insights into healthy diet or innovations in biotechnology and bioeconomics. Therein lies a great potential for added value, for example, by developing knowledge-intensive services and innovative research-based branches of industry.

To fully realise the potentials within omics technologies, several challenges are to be overcome during the next few years. This particularly includes coping with the technology-driven explosion in quantity of ascertainable molecular and physiological data. These developments in life sciences lead to new requirements for training young scientists, for the information technological infrastructure, for the networking of our universities and non-university research institutions, and for a sustainable funding of infrastructures.

This *Report on Tomorrow's Science* was prepared by a Scientific Committee at Leopoldina and is directed at science-related policymakers in national and federal state bodies, research organisations and scientists in academic institutions. It addresses the question of how life sciences in Germany can be structurally prepared for the rapid developments in omics technologies to guarantee sustainable and competitive research and training. It specifies key deficits and perspective challenges, and suggests future scenarios. This *Report on Tomorrow's Science* is borne of the conviction that the potentials of omics technologies can only be accessed under the umbrella of a new, national omics and IT infrastructure.



Prof. Dr. Dr. h. c. mult. Jörg Hacker
President of the German National Academy of Sciences Leopoldina

Content

Summary

At the start of the 21st century, life sciences are undergoing a radical change. Groundbreaking technologies are opening up entirely new possibilities of analysing life processes. Using omics technologies, different biomolecules, for example DNA, RNA, proteins or metabolites, can be detected in living organisms almost in their totality. Based on omics data, life sciences such as molecular biology, biomedicine or health research increasingly aim to obtain a computer-assisted observation of molecular processes and thereby a new understanding of life processes.

The new technologies generate huge quantities of data of which only fragments can be analysed at present. This generates the so-called *Big Data* problem as the surge in data quantities does not automatically mean a greater knowledge acquisition. The challenge is to extract and analyse information from the wealth of digital data that is relevant to the respective scientific issue. Moreover, the data and the findings derived from this data need to be made available to the scientific community using suitable networks requiring close interdisciplinary collaboration between life sciences and other scientific fields such as informatics, mathematics, physics and engineering.

This *Report on Tomorrow's Science* presents a clear diagnosis: Germany is not adequately prepared for the rapid developments in omics technologies, particularly the information technology requirements of these technologies. Visionary research funding programmes once led to the internationally visible and competitive development of genomics, bioinformatics and systems biology in Germany. Yet these partially very cost-intensive branches of research are in danger of collapsing without long-term financing strategies or sustainable integration into existing structures. This can result in losing the connection to rapid developments in research and training internationally (e.g. US, Switzerland, Great Britain) in the near future – a development with a strong negative impact on the attractiveness of Germany as a location for science and development. Modern medicine would also be affected in terms of its competitiveness in emerging developments in clinical diagnostics and therapy.

This *Report on Tomorrow's Science* uncovers the following structurally related deficits in life sciences:

- The development of major potentials within the new technologies will be limited due to the lack of transitions in our science system between institutions, stages of training and career as well as university and economy. The necessary close connection of research, training and infrastructure between universities and non-university institutions is too rarely guaranteed.

- As a result of statutory regulations (Section 91b of the German Basic Law), only non-university institutions may be co-financed by the federal government on a permanent basis, therefore they have a greater opportunity to develop and maintain cost-intensive research infrastructures. To universities these infrastructures are almost exclusively accessible on the basis of specific project collaborations.

- The federal states alone cannot cover the high costs of maintaining and developing university infrastructures to use omics technologies adequately. Due to the lack of basic funding, universities lose the connection to technical developments. They cannot afford the purchase, continuous operation and the necessary continuous replacement costs of the expensive large equipment for omics analyses. Yet without a state-of-the-art infrastructure, universities cannot carry out modern research and teaching.

- The present and future bioinformatics requirements of life sciences are severely underestimated. Therefore, even in the major non-university research institutions there is a lack of adequate information technology capacity to cope with the quantity of acquired data. There are neither enough trained bioinformaticians nor enough life scientists with bioinformatics expertise. For young scientists with the respective qualifications, there are too few attractive career paths within academic research. By limiting the duration of contracts for highly qualified scientific personnel, institutions face a continual loss of valuable expertise.

- There is a lack of a national comprehensive strategy for the sustainable promotion and development of the omics-driven research and technology sector in Germany.

This *Report on Tomorrow's Science* recommends acting now to set the course for structural innovations. The development of a national omics and IT infrastructure plays a key role in this context. Organisational scenarios are proposed in which this infrastructure is distributed to various centres, each specialised in a certain research area, and managed by a coordinating committee.

The "DFG scenario" is based on expanding this organisation's range of responsibilities. The German Research Foundation (Deutsche Forschungsgemeinschaft – DFG) could support the development of a distributed national omics and IT infrastructure by setting up a DFG panel for omics technologies, by founding DFG-maintained Central Research Facilities and by founding a DFG Senate Commission for high-throughput technologies and bioinformatics in life sciences. This inter-institutionally set up Senate Commission would regulate access to these centres and, in consultation with the universities and non-university organisations, would be suitable for developing and coordinating the proposed national omics and IT infrastructure with centres operated by different bodies.

The "Swiss scenario" follows the model of the federative organisational structure of the Swiss Institute of Bioinformatics (SIB). In this case, the set-up of the national omics and IT infrastructure would be placed in the hands of a newly founded, legally and financially independent organisation, which would take on the long-term coordination and development.

Partial aspects of both scenarios are compatible with each other. Therefore, it is also worth considering the combination of these scenarios in order to create an effective overall structure. In both scenarios the demand-based development of large, technology-specialised and subject-focused national research centres and the incorporation of existing ones are feasible additional options.

Independent of the respective scenario, sustainable funding and a flexible access concept are indispensable for the pursued infrastructure. The aim of this national omics and IT infrastructure is to permanently enable scientists, irrespective of which institution they belong to, to gain access to state-of-the-art technology and technical expertise in their region and in all of Germany at the highest level. The outlined scenarios are focused on the situation in Germany, however they should not be considered in isolation from the European and international context. The German National Academy of Sciences Leopoldina hopes to initiate with this *Report on Tomorrow's Science* a broad discussion on the future sustainability of life sciences research in Germany.

1 A technology-related paradigm shift in life sciences

Since the discovery of DNA as the hereditary material, life sciences have been heading towards a new understanding of life processes.[1] The deciphering of a genome, i. e. the complete set of an organism's genes, was first successful in 1995, when the complete genome sequence of the bacterium *Haemophilus influenzae* was published. Only six years later the virtually complete genome sequence of humans was decoded. Using the sequence of about 3 billion letters (nucleotides), scientists hoped to have in their hands the long sought-after key to understanding the complex human organism. However, it quickly became clear that deciphering the genome sequence was only the first major step, as the manifestation of genes depends on several environmental factors and a complex interaction of genes with each other and the environment. To clarify these interaction networks scientists are increasingly using newly developed bioanalytical high-throughput methods, so-called "omics". Using omics-based systems biology the aim is to comprehensively describe molecular processes in living systems and to understand these processes at a greater level of precision.[2] This shift in paradigm in life sciences is taking place at several levels: these include novel ways to measure biological process operations, a focus on experimental work that is determined by technology and the generation of huge datasets that require life sciences to be increasingly mathematised.[3]

The high-throughput methods generate extensive qualitative and quantitative data, for example, of gene sequences (genomics), epigenetic modifications (epigenomics), RNA transcripts (transcriptomics), proteins (proteomics) and metabolic products (metabolomics). However, frequently not yet all molecules can be recorded and quantified. Only in the genomics, epigenomics and transcriptomics fields can genome-wide coverage be achieved at present. In the other fields both the analysis technologies and the data processing need to be yet further developed. Consequently, a virtually complete representation of the proteome has only been achieved so far in less complex microorganisms. For bacteria, genetic data can now be comprehensively linked to further data obtained from proteomics or metabolomics, which enables new insights into the structure and function of cellular networks. Especially in the metabolomics field there are, though, still considerable deficits in identifying existing metabolites and recording metabolic flows.

Existing technologies, or those in development are geared towards performing genome, epigenome, transcriptome, proteome and metabolome analyses at the single cell level. Moreover, detailed insights are expected into cellular differen-

1 UNESCO defines life sciences in the following way: "Life Sciences consist of biochemistry, bioinformatics, biology, biomedicine, biophysics, biotechnology and genetic engineering, food science, food technology, medicine, medical technology, pharmacy and pharmacology, environmental management and environment engineering" (see www.unesco.de/lebenswissenschaften.html; last accessed on 23 June 2014).

2 For an introduction into systems biology see the Federal Ministry of Education and Research (BMBF) 2002. The latest developments in systems biology since 2010 have been discussed in the research journal *systembiologie.de – The magazine for systems biology research in Germany* (see www.systembiologie.de).

3 From time to time, the described change in life sciences technology is also termed "new biology". It is found programmatically in the statement of the US-American National Research Council of the National Academies *A New Biology for the 21st Century* from 2009.

tiation processes, for example, in tumour cell development. On a molecular genetic basis, metagenomics now also analyses entire organism communities in their natural environment. Metagenomes and metatranscriptomes enable, for example, so-called "microbiomes" to be studied, which are important to our health, for example, as individual intestinal flora.

This all appears to describe a development in 21st century life sciences that is still in its infancy and which leads us to expect many more fundamental discoveries and innovations. This technological revolution will fundamentally change the structure of life sciences research, teaching and infrastructures.

2 Description of omics technologies

Definition

The complete set of all an organism's genes is called a gen**ome**, the complete set of epigenetic modifications an epigen**ome**, the complete set of RNA transcripts a transcript**ome**, that of proteins a prote**ome** and that of metabolites a metabol**ome** etc. Talking about research into the respective "**-omes**", the syllable "**-ics**" (English) is attached: Gen-om-**ics**, where the syllable "**-ome**" emphasises the scientific aspiration to record and describe as completely as possible the respective level of life processes.[4]

Omics technologies as bioanalytical high-throughput analysis techniques have become indispensable tools of today's life sciences research. In a largely automated process and in a relatively short period, they permit the parallel, comprehensive analysis of biomolecules of a biological sample, whereby generally only the combination of different omics technologies can complete the picture of the life process to be studied. As a result very large data quantities are obtained which can only be filtered, processed and evaluated in an integrated approach using high performance computers and bioinformatics.

Genomics

The genome denotes the complete set of genes, i. e. the hereditary information of a living being, which is recorded in a double-stranded helix structure of deoxyribonucleic acid (DNA). DNA consists of four different nucleotides which each contain one of the four organic bases adenine, thymine, guanine or cytosine. The order of these bases is called the sequence and determines the blueprint of the proteins, for example. The length of genome sequences ranges from less than a million for certain bacteria to up to several billion for higher animals, plants and humans. Recording these sequences quickly and completely has been facilitated substantially by the development of high-throughput sequencing machines. Whereas the first deciphering of a human genome (about 3 billion base pairs) took a good decade and cost several billion US dollars, modern DNA sequencing machines now make it possible to completely decipher a human genome in a few days at a price of a few thousand US dollars.[5] Nowadays, recording complete genome sequences of any organism does not generally present a major problem. However, it is much more difficult to determine the arrangement of genes and their function. This requires protein-encoding genes and genes that just encode RNA to be distinguished. The identification of sequence patterns associated with gene regulation also represents an often unresolved problem. Genome sequences are analysed using bioinformatic methods. Using sophisticated programme packages, smaller microbial genomes can already be extensively automatically annotated, i. e. evaluated in

4 See Lederberg/McCray 2001. The rapid spread of "omics" terminology is now also viewed critically (see Hotz 2012). By now several new omics fields have differentiated themselves, which for example study the modification of gene expression through methylations (epigenomics), the interactions of biomolecules in the cell (interactomics), the microorganism communities colonising humans (microbiomics) or the dependency of medication efficacy on the genetic configuration of patients (pharmacogenomics).

5 See www.genome.gov/sequencingcosts/ (last accessed on 23 June 2014). It is expected that costs will be reduced to below 1000 US dollars, see the announcement from Illumina (www.bio-itworld.com/2014/1/14/illumina-announces-thousand-dollar-genome.html; last accessed on 23 June 2014).

Omics in medicine: customised diagnostics and therapies

Extensive molecular genetic analyses already play a vital role in the diagnostics and treatment of genetically determined hereditary diseases, in oncology and in the treatment of viral diseases such as HIV or HPV.[1] Omics technologies such as transcriptomics have also found their way into everyday clinical practice. As a result of the decreasing costs of whole genome sequencing it is expected that omics technologies will soon be widely used in medicine, in particular for diagnostics and prediction. By comparing samples of healthy and ill people, clinical research work endeavours to identify and develop so-called molecular biomarkers. This requires the exact definition of patient populations by means of a precise, reproducible investigation of the phenotype and access to a large number of relevant patient samples. Biomarkers being objective measurement parameters for describing normal and pathological biological processes are supposed to be used for targeted therapy selection and also in clinical studies. For several years now, in genome-wide association studies using DNA microarray technology, statistical correlations have been sought between genetic and phenotype disease-related data. It is hoped that this will help to increasingly define molecular causes for diseases. This opens up customised preventative, diagnostic and treatment methods with high efficacy whilst at the same time minimising side effects, a development which is called "personalised" or also "individualised medicine".[2]

1 HIV stands for Human Immunodeficiency Virus, HPV for Human Papillomavirus.

2 An academic group under the direction of Leopoldina is currently working on a report on this topic.

a few hours. It is much costlier, however, to analyse genome sequences of higher developed organisms such as plants, animals and humans.

Transcriptomics

Using transcriptomics, the complete set of all transcripts (transcriptome) of a defined cell type is analysed at a certain point in time. Transcripts are ribonucleic acids (RNA) produced during the transcription of genes and thereby reflect the genes' activity level. The transcriptome is highly dynamic and greatly depends on environmental factors acting on the respective cell type. One of the main tasks of transcriptomics is to elucidate gene regulation, i. e. to work out the molecular regulatory mechanisms that control gene activity. In addition to protein-dependent gene regulation, gene regulation via small RNA molecules also plays a significant role. Until recently transcripts were almost exclusively detected using DNA microarray technology. This technique involves the specific single detection of different RNA molecules in a compact area (chips) using sequence-specific recognition. Recently, RNA sequencing (RNA-Seq) has gained increasing importance because using this technique enables the identity and quantity of existing RNA molecules to be detected at a high level of precision and new functional RNA classes to be identified. Using RNA-Seq it is now possible to analyse the transcriptome of single cells and also the metatranscriptome of complex microbial communities.

Another type of gene regulation is the result of epigenomic modifications. Epigenomics investigates changes in gene expression that are caused by regulatory mechanisms which do not lie within the actual DNA sequence. This gene "programming" is determined by chemical modifications of the DNA itself (e.g. methylation of cytosine) or of DNA-binding proteins. This opens up new levels of analysis for functional genome research and is expected, for example, to provide a new way of understanding complex diseases.

Proteomics

Using proteomics the complete set of all proteins (proteome) of a cell type is recorded at a certain point in time. Whereas the genome of an organism is relatively stable, the proteome, like the transcriptome, is highly dynamic. Fully understanding the process in its structure, dynamic and function, from the biosynthesis of the proteins to organising the fragile protein super network, may be one of the greatest challenges of molecular cell biology in the next few years.

Two milestones in particular should be mentioned in relation to the tremendous advancement in proteome analysis in the past 15 years. Firstly, the successful development of highly sensitive mass spectrometry techniques was achieved, particularly the possibility of using mild ionisation methods to convert peptides (defined protein fragments) into gaseous ions to then accurately determine their molecular mass. Secondly, the complete sequencing of genomes and the amino acid sequences of proteins derived from this sequencing was the basis for conclusively correlating genes and proteins. Using mass spectrometry it is now possible not only to identify the majority of the proteins formed in a bacterial or yeast cell, but also to quantify them. The approximately 23,000 protein-coding genes of humans are translated as required within the different cell types by mechanisms such as alternative splicing, processing and post-translational chemical modifications into potentially more than one million functionally different proteins. At present, it is still not possible to comprehensively record these. Current work is also focused on methods to establish the protein equipment of entire organism communities (metaproteome). The results of metaproteomics lead, for example, to entirely new impulses for elucidating ecological or medical issues. Major advances are achieved in the development of highly sensitive and specific imaging

Omics in biotechnology: developing tailored bacterial production strains

In biotechnology, the synthesis potential of microorganisms is used to produce useful organic compounds. In this way *Corynebacterium glutamicum* produces large quantities of the amino acid lysine, which is used as a feed supplement. *Xanthomonas campestris* provides the thickening agent xanthan gum, which is widely used in the manufacture of cosmetics, pharmaceuticals and foodstuffs. *Actinomycetes* produce a multitude of medically efficacious substances, for example, acarbose, an active pharmaceutical ingredient that is used to treat type 2 diabetes mellitus. Of great importance to the quality and cost-effectiveness of the production processes are optimised production strains, which in each case synthesise the required product, preferably in large quantities. Until a few years ago, production strains were exclusively developed using a method based on mutation and selection. Using omics technologies, cellular biosynthesis processes can now be analysed in detail so that it is possible to develop strains in a targeted manner, in which the biosynthetic steps are rationally optimised. This method is known as *metabolic engineering*. This field is developing rapidly at present on the basis of genome-based systems biology and in future it will be increasingly characterised by the use of synthetic gene building blocks.

Omics in plant research:
metabolomics for resilient and productive crops

On the one hand, plants contain primary metabolites (e. g. starch or amino acids), which are necessary for development and reproduction, on the other hand, secondary metabolites (e. g. menthol or nicotine), which are essential for the process of adjustment to variable environmental conditions or for the defence against pathogens and natural enemies. Secondary metabolites are subject to a vast structural and functional diversity. It is estimated that there are 4,000 to 20,000 different metabolites per plant species and the more than 100,000 botanical secondary metabolites known to date probably represent just a fraction of the total number. Often the biosynthetic pathways of these substances, their cellular arrangement and temporal patterns of appearance are highly complex. Omics-based research helps to identify the involved genes and enzymes to create metabolic maps of the plants. There are also efforts to use omics technologies to find new metabolites and to better understand the interaction of crops with their environment. Metabolome analyses make it possible, for example, using so-called metabolic markers, to characterise in detail the appearance (phenotype) of cultivated or naturally occurring variants of a plant species. Using this as a basis, a sound selection can be made for further breeding, for example, to make potato plants more resistant to pathogens and abiotic stress factors, such as drought or to increase their nutritional content.

methods and their automation. Therefore, molecular imaging, which enables the quantity and position of certain molecules (particularly proteins) to be visualised and localised in living cells or tissues, has become an indispensable element of omics-driven research.

Metabolomics

Metabolomics enables the comprehensive quantitative and qualitative analysis of all metabolites (metabolome) of a defined cell type or tissue sample. As a result of the biochemical diversity of sugars, fatty acids, amino acids, alcohols etc. and the partially very different concentrations of these metabolites in biological samples, metabolic analyses are generally associated with great bioanalytical challenges. This also lies in the fact that different methods for detection, quantification and structure identification are required. Mass spectrometry and nuclear magnetic resonance spectrometry (NMR) are predominantly used. The development of increasingly sensitive mass spectro-meters and linking them to gas or liquid chromatography has led to a significant development of metabolomics in recent years. Entirely new bioinformatic methods and databases for data analysis and interpretation and for linking genome, transcriptome and proteome data for systems biological approaches have also been developed. The greatest challenges in the metabolomics field are currently in precisely identifying the given measured substances, recording metabolic flows, quality control and standardising methods and measurement parameters.

3 Previous and current funding measures for the new developments in life sciences

3.1 Omics technologies and systems biology

Since the mid 1990s, the Federal Ministry of Education and Research (BMBF) has made a significant contribution to setting up omics-based and systems biology projects and institutions. The funding measures to date have led to clear progress in German omics-based research and systems biology. The funding primarily supported the following projects: the German Human Genome Project (DHGP, 1996–2002), New Methods for Functional Proteome Analysis (2000–2006), the National Genome Research Network (NGFN, 2001–2013), Genome Research on Microorganisms (GENOMIK, 1999–2012), the German Plant Genome Research Programme (GABI, 1999–2012) and the Functional Genome Analysis in Animal Organisms (FUGATO, 2000–2012). As part of the NGFN, the German Resource Centre for Genome Research (RZPD) was set up, which existed from 2000 to 2007 but was shut down once funding had run out.[6] From 2004 to 2018 the BMBF is particularly supporting systems biology, from 2012 with specific further developments in the fields of systems medicine and systems biotechnology. In addition to national funding measures (e. g. SysMO, MedSys, CancerSys, GeronSys, FORSYS), the BMBF is also involved in European (ERASysAPP – ERA-Net Systems Biology Applications)[7] and international (e. g. INREMOS in the biotechnology field) initiatives. Since the mid 1990s the BMBF has invested about 1.5 billion euros in German research funding programmes in the field of genome research and systems biology.[8] In 2012 the BMBF started the German epigenome programme (DEEP) which is funded until 2017 with 20 million euros and which forms the German participation in the International Human Epigenome Consortium (IHEC).

Due to these BMBF initiatives, genomics is very well developed in Germany, though the BMBF-funded projects do not include any basic financial security and discontinue at the end of the funding period without, for example, sustainable financing strategies or integration in existing structures being ensured for the established infrastructures. The federal states in which the respective university institutions are based are seldom in the position of providing the basic financial security. The expiry of several national BMBF-funded programmes in 2012 or 2013 raises the pressing question of how the cost-intensive technologies for omics research and systems biology can be continued in the future and above all, how a collapse of the BMBF-developed structures can be prevented after losing funding.

The federal government and states also support omics technologies and systems biology directly via the non-university research organisations for which they jointly provide basic funding. The programme-oriented Helmholtz Association of German Research Centres (HGF)

6 The work of the RZPD, which was founded as a non-profit organisation, was subsequently continued by two private companies, ImaGenes GmbH and ATLAS Biolabs GmbH.

7 ERASysAPP is the successor programme to the ERA networks ERASysBIO and ERASysBIO+ (see BMBF 2013a).

8 BMBF notification from January 2014.

owns key national and international infrastructures for omics technologies such as at the German Cancer Research Center, Heidelberg (DKFZ), at the Helmholtz Center Munich – German Research Center for Environmental Health (HMGU) or at the Max Delbrück Center for Molecular Medicine (MDC). The HGF has founded a Helmholtz alliance *Systems Biology*, in which university and non-university institutions are involved. The Berlin Institute for Medical Systems Biology (BIMSB) is entirely dedicated to this research approach. Furthermore, the German Centres for Health Research collaborate across Germany with university medicine, in which bioinformatics-supported omics technologies and systems biological approaches are also used. In programme-oriented support there is also an interdisciplinary initiative *Personalised Medicine* with joint use of technology platforms, an IT and systems medicine platform and joint training activities. The omics-specific support strategies of the HGF lie in strengthening collaborations, primarily with university partners, promoting young talent and ensuring infrastructures.

The Max Planck Society (MPG) supports the development and use of omics both in individual departments (e.g. the Department of Proteomics and Signal Transduction at the Max Planck Institute of Biochemistry), in entire Max Planck institutes (e.g. Max Planck Institute of Molecular Genetics) and in central sequencing facilities (e.g. in Berlin and Cologne), which are used by several Max Planck institutes. Nevertheless the orientation towards flexible and free fundamental research does not enable sustainable omics structures to be set up and made accessible within the MPG beyond its own needs for university research in Germany.

The research infrastructures and research-based services of the Leibniz Association (WGL) are closely linked to university locations. The majority of institutions uses omics technologies, systems biology plays a part in the research associations of biodiversity, sustainable food production and healthy nutrition, healthy ageing, interdisciplinary active drug research and biotechnology. At some locations (e.g. Jena, Braunschweig) omics technologies are already being used jointly by Leibniz institutions and neighbouring universities. It is possible to use them for university research and teaching as part of research associations, science campuses and collaborations.

The Fraunhofer-Gesellschaft (FhG) is also active in the omics technologies and systems biology fields. As part of the Fraunhofer *Life Sciences* Alliance, medical translation research and biomedical engineering, for example, are funded. As with other non-university institutions, access to the infrastructures by external researchers is primarily possible via project collaborations. These currently exist in various fields such as systems biology, oncology, immunology, biochemistry, microbiology and bioinformatics.

Information on the level of development of omics and systems biology at German universities is much more difficult to gather. The infrastructure for omics-based genome research and systems biology has been largely set up by third-party funding (BMBF, German Research Foundation – DFG, EU etc.), even if federal states directly support this process at some universities or indirectly by including universities into existing infrastructures. Bavaria, for example, has set up the Bavarian Network for Genome Research (BayGene) and the Bavarian Research Network for Molecular Biosystems (BioSysNet). In the event of available resources and corresponding profiling, universities can promote the emphasis in these fields themselves. The Ludwig-Maximilians-Universität has a Gene Center, at the Technische Universität München the Bavarian Biomolecular Mass Spectrometry Center (BayBioMS) was set up. The state of North Rhine-Westphalia funded the Centre of Biotechnology (CeBiTec) at Bielefeld University, which operates a platform for omics technologies. In Baden-Württemberg the Center for Biosystems Analysis (ZBSA) in Freiburg and the Center for Quantitative Biology (Bioquant) in Heidelberg were set up using funds from the Baden-Württemberg Foundation and those universities involved. In Kiel the medical faculty has a large technological platform for genomics and systems biology in a clinical context. The University of Göttingen founded the Göttingen Genomics Laboratory. The states of Lower Saxony and Mecklenburg-Vorpommern are involved in the Northern German Center of Microbal Genomics (NZMG), a network of distributed infrastructures initiated by Göttingen and Greifswald, in which university and non-university institutions (WGL, HGF) make available all omics technologies relevant to microorganisms in Germany and plan joint activities in research and training.

Omics technologies and systems biology at universities are also jointly funded by the federal government and states via the DFG. The largest German research funding organisation for university research does not, however, so far have its own strategy for the specific funding of omics technologies and systems biology at universities. Previously, clusters of excellence and collaborative research centres have been supported as part of large equipment initiatives and graduate training, for example, the *Quantitative Biosciences* graduate school in Munich or the *Computational Systems Biology Research Training Group* in Berlin. The DFG funding programmes (e.g. large equipment initiatives) favour a decentralised infrastructure with a relatively large number of locations. The DFG also supports the establishment of *core facilities*, the opening of which for external users often proves to be difficult in practice. A further problem is that not all universities can afford to maintain a research infrastructure because the costs for the ongoing operation and maintenance can greatly exceed the purchase costs in the long run. Consequently only a few universities have so far been able to set up and maintain large-scale omics structures on a long-term basis.

3.2 Bioinformatics

All omics methods or the evaluation of their results are reliant on powerful and competent bioinformatics support. Bioinformatics in Germany was specifically funded in the 1990s to make it competitive and to gear it towards the new omics-driven research fields. From 1993–1997 the BMBF funded *Molecular Bioinformatics* and the DFG priority programme *Informatics Methods for the Analysis and Interpretation of Large Genomic Datasets* ran from 1999–2005. A DFG initiative on bioinformatics (2000–2006) contributed to the establishment of various bioinformatics sites in Bielefeld, Munich, Leipzig, Saarbrücken and Tübingen. For five years a total of 25 million euros was available for this.[9] At the same time six bioinformatics centres were funded by the BMBF from 2001–2006. The BMBF also funded a Helmholtz Network for Bioinformatics. The HGF is now continuing to invest independently in the bioinformatics field and is trying to create a joint platform for data integration, for example, at HMGU.

The other non-university institutions are also committed to setting up bioinformatics infrastructures and bioinformatics research. The Max Planck Institute for Informatics in Saarbrücken has a department for Computational Biology and Applied Algorithmics, the Fraunhofer Institute for Applied Information Technology (FIT) has a research department for Life Science Informatics. The Institute for Information Infrastructure (FIZ) of the

9 See Lengauer 2008, p. 224.

Leibniz Association is dedicated to setting up information infrastructures, which also involves the long-term handling of large quantities of research data in Germany. Directed by the Leibniz Association, more specifically the FIZ, the Commission on the Future of Information Infrastructure prepared in 2011 an *Overall Concept for the Information Infrastructure in Germany*. This study reveals "that various scientific organisations such as individual Leibniz institutes or Max Planck institutes and Helmholtz centres have each set up data centres for their data driven by different specialist disciplines. However, at present it cannot be assumed, for example, that data from university research is secured and made available in these data centres in the long term. For this reason it would be a key qualitative step if the GWK would ask these institutions and equip them with the relevant resources to fulfil the task of data protection on a national scale."[10] These remarks show that at present there is hardly any coordinated data protection concept operating Germany wide.

Internationally renowned centres such as the Joint Genome Institute (JGI)[11] and the Broad Institute[12] in the US, the European Bioinformatics Institute (EBI) in Great Britain[13] or the Beijing Genomics Institute (BGI) in China[14] are globally visible centres for the generation, collection and bioinformatics supported evaluation of omics data. Germany barely has anything comparable to offer.

The Science for Life Laboratory in Sweden is the national research institution for large-scale research in molecular biology and bioinformatics. The Swedish Wallenberg Foundation has provided 25 million euros for the centre.[15] In Great Britain about 30 million pounds is invested in setting up a central data centre in Oxford.[16] In Switzerland, the Swiss Institute of Bioinformatics (SIB) connects decentralised research groups located in universities with one centralised management and offers support for infrastructures as well as specialised personnel. It also has data centres such as the Vital IT Center in Lausanne, which performs data evaluation for several universities. The SIB is permanently financed by more than a third through federal funds.

In comparison, since the last funding initiative in 2005, bioinformatics in Germany has not been specifically funded or adapted to new developments. Local and national resources to support a bioinformatics infrastructure are generally not funded in the long term.[17] The BMBF initiatives published in 2013 on big data and the appeal to set up a German Network for Bioinformatics Infrastructure are heading, in fact, in the right direction but it must be ensured that the budget is adequate to cover the existing immediate need in Germany and to achieve sustainability.[18]

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10 Commission on the Future of Information Infrastructure 2011 p. 65. GWK stands for the Joint Science Conference (Gemeinsame Wissenschaftskonferenz).

11 The Joint Genome Institute had a budget of about 69 million US dollars in 2011 and 2012 (see U.S. Department of Energy – Joint Genome Institute 2011, 2012a).

12 The Broad Institute is operated jointly by Harvard University and the Massachusetts Institute of Technology.

13 117 million euros is invested in setting up the ELIXIR hubs and nodes, 90 million euros comes from the Department for Business, Innovations and Skills' Large Facilities Capital Fund (LFCF) (see European Molecular Biology Laboratory – European Bioinformatics Institute 2012, p. xviii).

14 The BGI is one of the world's largest sequencing centres (see Ropers 2013), financing figures are not publicly accessible.

15 See Karolinska Institutet 2012.

16 See Gibney 2013.

17 In 2012 the BioEconomy Council already presented the *Requirements for a Bioinformatics Infrastructure in Germany for Future Research with Bio-economic Relevance* (see BioEconomy Council 2012).

18 This network, which is financed by the BMBF, should consist of six service centres and be managed by one coordination unit composed of representatives of the service centres. The coordination unit has the task of developing research infrastructures at universities, regulating access to the centres, driving forward interdisciplinary training, including business and ensuring a link to existing national and international organisations. In a period of five years about 22 million euros should be allocated to the participating service centres (see Federal Ministry of Education and Research 2013b).

3.3 Conclusion

At a national level and in a number of federal states there has already been significant support for omics technologies, systems biology and bioinformatics and in some cases this is also being continued. As a result of the investment that has been made, German genome research currently occupies a leading position in some fields (e.g. cancer research, microbiology, plant research) compared to the rest of Europe. However, the essential BMBF funding programmes or excellence initiatives for this have expired or will expire without any sustainable follow-on concepts for integration into existing structures or new financing arrangements with federal participation. The individual institutions of the non-university research organisations are not generally linked to each other and are only partially accessible to external users as part of specific project collaborations. The position of universities in these technology-intensive and rapidly developing research areas can only be described as internationally competitive in exceptional cases. The sustainability of the research infrastructures is only secured for universities to a minor extent whereas the non-university institutions are developing strategies independently of each other for using omics technologies and setting up bioinformatics structures. It is symptomatic of the imbalance in the German scientific system that in the first *Genetic Engineering Report* published in 2005 of the Berlin-Brandenburg Academy of Sciences and Humanities as the fifth most capable genome research centres, which formed the core of the National Genome Research Network, only non-university institutions were named: four institutes of the Helmholtz Association (DKFZ, HZI, HMGU, MDC) and one institute of the Max Planck Society (MPIMG).[19] This illustrates that predominantly non-university institutions, as a result of the constitutionally permitted institutional support by the federal government, possess the pre-requisites of occupying a prominent role in this network.

19 Berlin-Brandenburgische Akademie der Wissenschaften 2005, p. 61f.

4 Structural challenges in the organisation of life sciences

4.1 Research infrastructures at universities

The German scientific system has a high level of differentiation: it is sub-divided into universities, non-university research institutions and research funding organisations. The federal government and federal states jointly fund the major non-university research institutions such as the Max Planck Society (MPG), the Fraunhofer-Gesellschaft (FhG), the Helmholtz Association (HGF) and the Leibniz Association (WGL). No permanent institutions at universities can currently be set up using federal funds as this is not permitted constitutionally (Section 91b of the German Basic Law). This means that the technological distance between universities and non-university research institutions is gradually increasing because often the states do not have the resources to ensure sufficient basic funding for the universities. Consequently, universities have serious problems to adequately finance teaching, research and infrastructure.[20] It is asking too much of many federal states to sustainably finance infrastructures to use omics technologies.

Financing infrastructures via third-party funded projects of the DFG, the BMBF or the EU has the serious disadvantage of not being long-term support. Large pieces of equipment are almost exclusively purchased with third-party funds in fixed-term research projects, without the operating costs being met to any appreciable extent. As the fixed rates for administrative costs (overheads) are generally not added in full to the projects but are more or less used for non-project related purposes, these funds do not generally make it possible to purchase and maintain newly developed successor equipment on a broad scale. The infrastructure problem at universities continues to exist.

4.2 Broad access to omics technologies for universities

Universities take on the task of training students in the broadest sense: from Bachelor's via Master's to PhD courses. Without access to new technologies, however, it is impossible to provide up-to-date basic training in modern life sciences. As a result, a great many Bachelor's and Master's degree graduates will have insufficient or no knowledge of omics technologies or bioinformatics. Furthermore, how can primarily small research groups whose universities do not have adequate omics infrastructures and are also not able in the medium term to develop these, gain access to existing infrastructures? Until now, access to such institutions has been predominantly based on specific project cooperations. The most problematic issue with this situation is that university researchers with innovative proposals are reliant on finding suitable or interested cooperation partners at non-university institutions. This is not always possible, particularly as part of programme research where individual research rarely finds a place. These conditions particularly impede the broad fundamental life sciences research at universities. Due to the nature of this research,

20 See the Leopoldina Discussion Paper *The Sustainability of the German Science System* (Leopoldina 2013).

the sometimes diverse possibilities of future applications are hardly predictable.

4.3 Setting up a strong IT infrastructure and bioinformatics

Bioinformatics is now one of the greatest challenges in the development of omics research. Research based on omics data requires adequate bioinformatics capacities and new methods for evaluating data and networking. A fundamental deficit already lies in insufficient existing storage, analysis and transfer capacities for data. Locally generated raw data is often too large for full transmission in a global network. The data, which is often stored at different locations, and the resulting knowledge models, however, need to be linked to each other. There is a multitude of databases that are organised in different ways: primary data, annotated data, topic-specific surveys etc. In addition, the software development for evaluating the data often lags behind the issues and technical development, and the numerous software solutions for data processing, which have been produced independently from each other, make it difficult to compare data. The networking of locations is currently not adequately ensured to benefit from the developments taking place at many locations (e.g. software developments, database setup). Joint coordination and technology distribution are therefore key tasks.

4.4 Including business in life sciences research

The availability of some very efficient bioanalytical services by industry makes it – from an economic point of view – increasingly reasonable to outsource certain omics technologies. However, this is currently only sensible for standardised and quality-assured methods such as DNA and RNA sequencing. The expertise for the respective technology must be retained in the research institutions at all times because this is a vital pre-requisite for analysing and evaluating the purchased services or data. Furthermore, the development of niche applications that are highly significant to scientific progress, such as single cell sequencing, often takes place in an academic research context and would arguably remain absent if entirely outsourcing genomics and transcriptomics to industry. For proteomics and metabolomics especially, even partial outsourcing is not sensible at present because the required standardisation of sample analysis in these fields is not yet given. In addition, the planning of measurement and subsequent annotation of data, for example the clear identification of a chemical substance or a protein, generally requires a very high level of specialist expertise that cannot be provided by technical personnel alone.

4.5 Interdisciplinary training in omics and bioinformatics

The omics-driven systems biology approaches require broad interdisciplinary training. But are students adequately prepared during their training for these demanding tasks of technology-driven developments in life sciences? And how should training at universities be organised so that enough students are adequately trained and acquired for research or demanding roles in industry?

To obtain a representative picture of the current training situation in Germany, a national survey of all life sciences, including medical, faculties was carried out as part of this report on the topic of omics technologies in teaching, training and infrastructures. Medicine was included in the university survey because the interface between systems biology and medicine will gain importance in the future.[21]

21 In life sciences, Master's programmes were polled, in medicine, medical study courses (n=229). The response rate overall was 49 per cent.

Evaluating this survey revealed that only a minority of all life sciences courses have a clear focus on omics technologies. The majority of these modules are optional courses whilst in the majority of medicine courses no omics modules are offered at all and the few that are offered are limited to theoretical introductions. Practical omics training is under-represented in life sciences including medicine. There are partial attempts in medicine to teach this content in some Master's courses, for example, for molecular medicine.

In terms of student numbers a very large deficit is apparent, especially in bioinformatics. The number of students in this field is so alarmingly low that there is no way they can cover the present and future requirement in this field.[22] This is not only due to a deficit in existing training capacities but arguably also because too few potential students are motivated to take a course in this field. The number of students in life sciences seems to be adequate in view of the demand, however the number of students with specialist training in omics and bioinformatics is too low.

In terms of providing more omics-specific teaching, physicians in particular are evidently aware of a deficiency in this area. However, as a result of the existing medicine licensure regulations, medicine offers few possibilities of including omics technologies in training. The question on omics-specific doctorate opportunities in medicine and other life sciences revealed that the percentage of PhD courses relating to omics is almost equally high in both fields at more than 80 per cent.

The expert discussions conducted as part of this report, highlighted in particular that general training problems lie in a lack of interdisciplinary expertise of students and teaching staff: The (bio)informaticians are too rarely introduced to omics-driven life sciences issues, the life scientists on their part frequently have too little knowledge of informatics and there are deficits in the knowledge of programmes for handling omics data and technologies. Relevant training, however, is not only a pre-requisite for several current research fields in life sciences, it is also increasing in importance in the field of industrial production and process engineering.

Similar problems emerge in medical teaching: Doctors need to be trained so that, above all, they have practical expertise. In this already very extensive and demanding training, the teaching of molecular biology principles is often too brief. This is a problem, in particular with regard to the increasing application of bioinformatics-based omics technologies in healthcare, because even now therapy decisions are frequently supported by computer programmes, so-called expert systems. This therefore raises the question of how to interest medical students in bioinformatics, systems biology or systems medicine and individualised medicine and how to integrate the associated practical training into medical studies.

4.6 Career options in life sciences and bioinformatics

At present there are not enough scientists and young scientists in the field of basic bioinformatics research. In addition, many researchers find highly attractive career possibilities in industry. The problem of jobs in scientific institutions correlates to the sustainability problem: many positions are financed by third-party funds and are therefore temporary. Employees' initial training takes a great deal of time and

22 This is not a problem that is specific to Germany or the life sciences. According to a report by the McKinsey Global Institute, in the US alone there will be a deficit of 140,000–190,000 experts in 2018 to analyse the growing datasets (see Manyika [et al.] 2011, p. 10–11, 104–106). This is particularly true for the bioinformatics field due to the massive growth in datasets and data complexity in life sciences.

because of the temporary contracts this process has to be repeated with new employees in a continuous cycle. In addition, as yet there are barely any career options at research institutions for IT specialists that deal with establishing and expanding infrastructures, further developing these and taking on coordinative roles. The use of new omics technologies needs a high degree of interdisciplinarity. If researchers are positioning themselves in frontier areas there is currently the risk that they will have no place in the German career system where, for example, in the medical field the positions are defined by the (largely organised by discipline) health services or by teaching. A lack of transparency in courses and career options as well as linguistic hurdles are also obstructive to foreign students entering these fields.

5 Scenarios of a national omics and IT infrastructure for research and training

To cover the future demand and remain internationally competitive, one should aim to substantially expand and strengthen omics-based research and training in life sciences that incorporate bioinformatics. The *Report on Tomorrow's Science* proposes developing a national omics and IT infrastructure. This should ensure access to high-throughput technologies and bioinformatics resources for scientists, irrespective of the institution to which they belong. It is particularly important to preserve what has already been set up and to further develop this in a coordinated manner. This national infrastructure will help to meet the following challenges:

- Creating and expanding the technical and information technology capacities in existing and new institutions
- Structurally linking omics research with bioinformatics
- Creating new concepts for access and use of omics technologies, including licences for accessing databases and software
- Supporting experimental implementation and subsequent data analysis
- Developing standards for data collection, processing, quality control and storage for improved comparability of data and facilitated data exchange
- Including omics technologies and bioinformatics in training
- Creating new personnel structures and career paths (e.g. increase research-based services in infrastructures)

These challenges concern all universities and non-university institutions that are active in omics-based research. For this reason, a coordinated approach of these institutions, taking into account their specific situations and structures, is vital to establish a national infrastructure. The added value of a national infrastructure is in being able to jointly overcome the outlined challenges, a task which cannot be achieved by any of the existing organisations alone. In particular, the organisation and integration of omics technologies must be achieved in context with bioinformatics, which is essential for these technologies. As a German Network for Bioinformatics Infrastructure[23] is currently being set up on the initiative of the BMBF, the omics infrastructure needs to be developed in very close coordination with the set-up of this bioinformatics network and, most importantly, sustainability needs to be ensured.

5.1 Future scenarios

Conceivable future scenarios for setting up a national omics and IT infrastructure require a nationwide network of distributed, subject-focused omics centres with bioinformatics expertise as a basic requirement. Within this distributed infrastructure, the participating centres would have to develop their own scientific-technological profiles. In a combination of research and service they should be geared towards

23 See Federal Ministry of Education and Research 2013b.

a specific technology and be focused on a topic, subject or be object-based (e. g. substance classes), thereby justifying the use and further development of certain technologies. Local sub-structures are well conceivable within the nationwide network. In this way universities and non-university institutions can jointly provide omics and IT resources in one location and develop a close cooperation in teaching and research. In addition, nationwide centres of university and non-university institutions that focus, for example, on groups of organisms or specific omics technologies may also be taken into account.

The centres should not be pure service providers which hold technologies without a subject or specialised focus but should be set up as far as possible around scientifically strong groups with the aim of focusing on scientific issues, including technology development. This should also ensure that the knowledge-intensive service always remains at the latest level of technical and scientific development. Despite the necessary diversification with respect to subject and technology, the centres need to remain flexible and open to the diversity of themes and subjects to be studied. The centres must provide omics technologies as well as bioinformatics expertise and develop these further.

In sub-areas, existing expertise should be incorporated in the network. Existing omics and IT centres should therefore be evaluated with respect to their quality and their contribution to the sought infrastructure. In the event that assessments reveal that the existing centres, even if they were upgraded, linked and coordinated, cannot adequately assure the nationwide requirement for omics and IT technologies, it is sensible to set up additional centres. Furthermore, universities with medical faculties should be evaluated with regard to their potential for upgrading existing or setting up new medicine-oriented omics centres.

The outlined network should offer the latest technologies and should be kept up to date. Funding of the technological networks needs to take into account that individual omics technologies differ greatly in terms of their investment volume and the dynamics of technological developments. Standard analyses, primarily in the field of genomics and transcriptomics, could be partially covered by a service model, for example by outsourcing to appropriate companies, whereas proteomics and metabolomics are much more reliant on centres and it is expected that this will continue in the medium term.

The DFG scenario

This scenario is based on established funding of the German Research Foundation (Deutsche Forschungsgemeinschaft – DFG) and proposes an expansion of this organisation's scope of responsibilities. The DFG could supervise the process of establishing and supporting a distributed national omics and IT infrastructure in the following ways:

(a) By setting up a DFG panel for omics technologies with its own financial backing for omics infrastructure and relevant projects. It should also to be possible to submit applications to this panel for individual projects that place emphasis on omics approaches.

(b) Founding DFG-maintained centres as part of the national omics and IT infrastructure that also ensures the sustainable support of research at universities. These centres could – similarly to the German research vessels *Meteor* and *Maria St. Merian* – be established as Central Research Facilities (see Box 1). The financing and operation of these centres would need to be ensured through special financing.

(c) By setting up a DFG Senate Commission for high-throughput technologies and bioinformatics in life sciences.

This inter-institutionally set up Senate Commission could regulate access to the omics centres.

(d) The DFG, via the Senate Commission and in consultation with university and non-university organisations, could take on the role for coordination and development for the national omics and IT infrastructure with centres operated by different bodies. It could organise the call for centres,[24] coordinate the network in consultation with the universities and non-university institutions and announce the existing capacities at the involved institutions in a transparent manner. Universities and non-university organisations could collaborate in ways similar to those established for the field of marine research in Germany (see Box 1). Centres of varying focus, size and administration could become part of the network and jointly harmonise their application and review processes. The network should be set up competitively and according to the bottom-up principle, i. e. via a call for centres that wish to participate in the national omics and IT infrastructure.

The DFG already funds *core facilities* at universities. The national omics and IT infrastructure is expected to make the funding measures of the DFG for research infrastructures in the life sciences more efficient and to allow running them in a strategically more coherent manner. Smaller sites located near centres could build up expertise in the fields of data analysis, sample preparation and bioinformatics, while they do not need to maintain the bulk of all technologies and concomitant highly specialised technical personnel.

24 The German Council of Science and Humanities could review the submitted applications as it has developed and successfully tested a science-based procedure for evaluating extensive research infrastructure projects (see German Council of Science and Humanities 2013).

The Swiss scenario

The responsibility of establishing a national omics and IT infrastructure could also be given to a legally and financially independent organisation that would need to be set up. The model for this scenario is the federative organisational structure of the Swiss Institute of Bioinformatics (SIB), that has been organising the bioinformatics infrastructure and data analysis in Switzerland since 1998 (see Box 2). An organisation following this model would be responsible for organising and coordinating the scientific as well as the technological setup of the national infrastructure and would need to develop user concepts and human resources for the various sites and centres across locations. Members of the organisation could (in contrast to the SIB model) all become institutions with relevant infrastructure or infrastructure potential. This scenario is compatible with points (a)–(c) of the DFG scenario so that consideration should also be given to a combination of the two models in order to create an effective overall structure.

In both scenarios it is possible to include existing, or to set up large, technology-specialised and subject-focused national research centres as needed – e. g. according to the known international models of the Joint Genome Institute (JGI) or the Beijing Genomics Institute (BGI) (see Box 3) – as an additional option as part of the outlined network of centres. A centralised development that assembles major resources in one location only should, however, be avoided as it does not follow the principle of federalism. For the viability of life sciences beyond programme research, it is of vital importance that effective structures for individual and basic research at universities are created. A balanced network of distributed centres therefore appears to be the most appropriate model to support an international competitive profile in research and teaching in various locations and regions across Germany.

BOX 1

Central Research Facilities – excellent infrastructures and service facilities for science

According to the DFG definition, a Central Research Facility is "an institution of national importance at which the high-quality staff and/or equipment required to provide scientific and technical services for research are concentrated at a single location. Such a facility is an important scientific research instrument for strengthening the research-relevant infrastructure of science and, consequently, represents a key prerequisite for preserving and raising the efficiency of research. In accordance with their role, Central Research Facilities are established long term."[1] The Central Research Facilities are non-university institutions of national importance. A sustainable commitment of the federal government in line with the requirements of the omics and IT infrastructure is possible in accordance with Section 91b of the German Basic Law.

German research vessels – research infrastructures for marine research

The German research vessels represent an excellent and internationally visible infrastructure for German marine research. The funding is sustainable because the annual cost for operation and technical personnel are covered. Currently, eight research vessels of varying size and equipment belong to the scientific research infrastructures for marine research. The investment costs for these vessels range from 11.8 million euros to 97.3 million euros.[2] Investors are the federal government and states, the owners are the BMBF, the states of Mecklenburg-Vorpommern and Schleswig-Holstein and the RF Forschungsschiffahrt GmbH Bremen. The annual operating costs are covered by the BMBF, individual states, the DFG and the HGF. The operators of the vessels are the HGF (Alfred Wegener Institute, GEOMAR) and the DFG. The two DFG-maintained research vessels *Meteor* and *Maria St. Merian* are set up as Central Research Facilities.

The research vessels are accessed by applications, which are submitted via the *German research vessels portal*.[3] For each vessel there is a body that plans the use of the vessels and a committee of experts that decides on the applications. Researchers from all academic institutions can submit applications. There is also the possibility of exchanging operating times between the vessels. The DFG Senate Commission on Oceanography decides on the applications for using the DFG vessels. KG Schiff, the Coordination Group for research vessels is a coordination committee for optimising the itineraries to avoid transit times.

1 See www.dfg.de/en/funded_projects/central_research_facilities/index.html (last accessed on 23 June 2014).

2 See German Council of Science and Humanities 2010, p. 50, 54.

3 See www.portal-forschungsschiffe.de/index.php?index=53 (last accessed on 23 June 2014).

BOX 2

The Swiss Institute of Bioinformatics (SIB) – the organisation for data analysis and data provision in a federal state

The coordination of bioinformatics at a national level is considered to be essential in Switzerland. For this purpose the SIB was founded as a private organisation already in 1998. Essentially it assumes two areas of activities: in the infrastructure and personnel field it provides bioinformatics core resources (maintenance of life sciences databases, software, web platforms, services, hardware, storage) and expertise for the national and international life science community. In the community building field it coordinates and represents bioinformatics in Switzerland and establishes expertise in bioinformatics research and teaching.

Renowned bioinformaticians with a professorship at a university, their own funding and who are active in bioinformatics research can apply for membership at the SIB. Associated group members will automatically become members of the SIB. Currently, there are 46 groups in 7 locations at 10 universities. Of the current total of 650 members, 200 people are directly employed by the SIB and 450 by universities. The advantage of such an organisational structure is that it ensures national collaboration and coordination whilst members perform their research and teach at universities.

Data storage and analysis in Switzerland is managed at a local and regional level. To accomplish this, the SIB is setting up data analysis centres in Switzerland such as the Vital IT Center in Lausanne. This centre performs data analysis for life science research of five universities. In addition, the SIB plans to set up the Basel Computation Biology Center, financed by the University of Basel and the SIB, to resolve the data handling problem in terms of infrastructure in other regions of Switzerland.

The SIB is financed from various sources: about a third comes from federal funds for research based on Section 16 of the Federal Law on Research. Another proportion of the budget comes from external research funds, which allow for a separate budgetary item for data analysis in their applications (so-called *bioinformatics consumables*).

5.2 Core elements of the future scenarios

Irrespective of the scenario that is ultimately put in place, the access, financing and link to European and international infrastructures as well as training and career possibilities need to be clarified. Depending on the scenario, the solutions may differ in the detail.

Access

Access to the technological and scientific resources of the national omics and IT infrastructure should be given solely on the basis of the scientific quality of the submitted projects.[25] Depending on the scenario, the design of the evaluation process would differ. A lean evaluation process should be developed in which researchers gain access

25 This also corresponds to the definition of infrastructures given by the *European Strategy Forum on Research Infrastructures* (ESFRI): "In all cases considered for the roadmap, these infrastructures must apply an 'Open Access' policy for basic research, i. e. be open to all interested researchers, based on open competition and selection of the proposals evaluated on the sole scientific excellence by international peer review" (European Strategy Forum on Research Infrastructure 2011, p. 7).

BOX 3

The DOE Joint Genome Institute (JGI)

The U.S. Department of Energy Joint Genome Institute was founded in 1997 and is a departmental research institute of the US Department of Energy, which combines the activities of three national laboratories (Lawrence Berkeley National Laboratory, Lawrence Livermore National Laboratory, HudsonAlpha Institute for Biotechnology). It has its own campus in Walnut Creek, California and is one of the largest and most prominent genome sequencing centres in the world. The institute is administered by the University of California. The JGI made a substantial contribution to the Human Genome Project. In accordance with the mission of the Department of Energy, the research focus of the JGI is in the fields of bioenergy, global carbon cycle and biogeochemistry. The JGI considers itself to be open to all users in the world, who can make applications to access the sequencing capacities. The JGI is going to actively train users of the centre.

The Beijing Genomics Institute (BGI)

The BGI is one of the largest genome sequencing centres in the world and was founded in 1999 as part of the Human Genome Project. At this institute numerous human, plant and animal genomes have already been deciphered to gain new findings for the health, agriculture and environment fields. The BGI also has branches outside of China in the US and Europe.

to the infrastructure. In the DFG and Swiss scenario, application and evaluation procedures should be standardised as part of the national infrastructure and access to the various centres should be regulated. Major projects should always be subjected to a review process as successfully exercised in existing technology centres (e. g. DESY – German Electron Synchrotron). Until the recommended national omics and IT infrastructure is set up, existing centres should facilitate access for external research groups also outside of project cooperations.

Financing

To sustainably develop omics technologies and bioinformatics, long-term financing of the proposed national infrastructure including maintenance and operating costs is indispensable. It would therefore be useful if this infrastructure was at least partially financed by the federal government in the long term. A further proportion could be contributed by the federal states or the participating universities. An additional key element of financing should be research projects in which a special budget is provided for those projects being carried out in the centres, for example within the scope of a DFG grant. In the DFG scenario, the DFG and the involved institutions should be allocated special funds that should not be charged to the existing funding schemes. Investments in omics research and bioinformatics in Germany are supposed to maintain these promising fields at an internationally competitive level.

International connection

The linkage to existing European or international infrastructures should be accelerated. Harmonisation of data which is required to efficiently exchange data should be promoted across Germany and connected to ongoing international and European projects. To administer data sustainably and without obstacles, international consensus on standardisation needs to be established. In the course of setting up a national omics and IT infrastructure, a German node for the ELIXIR project should be taken into consideration.[26]

Training

The national infrastructure should contribute to education and training in the omics and IT field. It is vital to have qualified and experienced personnel for the demanding teaching in these subjects. In order to establish diversified high-level courses a critical mass is needed not only from a technological point of view but also in terms of personnel. There are not yet enough locations at which students can be trained in omics technologies with integrated bioinformatics. One of the greatest deficits is that existing centres to date are poorly accessible to external users. Centres are largely only involved in the training of young scientists at the doctorate level. For this reason the national infrastructure needs to be closely linked to the training and advanced training of young scientists. Not every location can cover all aspects of training. Therefore, the training could be more efficiently organised across institutions in the state-wide network. If the relevant expertise is not available at a local university, in metabolomics for example, universities could be coordinated or supported via the national infrastructure for specialised or advanced education and training. The joint development of new courses is also conceivable. Furthermore, founding omics-based post-graduate schools or post-graduate academies located in the centres with open access to universities in the region could prove useful. The infrastructure could also be responsible for training highly specialised PhD students, who then further develop and spread the respective technology at their home locations.

Undergraduate training in omics technologies and bioinformatics is currently not granted to enough students to cover the future workforce requirement. It is recommended that universities place a greater focus on omics technologies and bioinformatics in life sciences training already in Bachelor's degree courses. Awareness of these subjects should preferably be promoted at Abitur (high school) level. To increase the number of graduates with expertise in omics technologies, systems biology and bioinformatics, additional Master's courses with a clear focus on these areas should be set up. To increase the number of students in such Master's courses, there should be an interdisciplinary admission procedure. Consideration should also be given to allowing graduates of universities of applied sciences (in German Fachhochschule) entry to university Master's courses. It is vital that students have omics expertise already at the start of a PhD course. Medical students should also be familiar with the technical possibilities of omics for generating and evaluating data, at least in theory and if possible in practice. This needs to be provided despite the rigid curriculum in medicine because therapy decisions are increasingly based on data generated using omics technologies.

Career options

Career options in the omics and IT field should be developed, including personnel positions for infrastructure set up and maintenance. As part of the national omics and IT infrastructure it is recommended that new positions are created to strengthen the reservoir of experts for new technologies. PhD students could work on omics-relevant equipment alongside their research and spend part of their time on setting up the infrastructure. As the tech-

26 The European EXLIR project develops the requirements for creating a sustainable infrastructure for information from life sciences and its translation into medicine, the environment, industry and society (see www.elixir-europe.org).

nology and particularly the evaluation of the generated data is very complex, these positions should only be filled by scientists that are specifically qualified for these tasks. For the research funding organisations this means that financing is required over extended periods so that more qualified scientists can be hired and kept for using, setting up and expanding the infrastructure. It is desirable to introduce career tracks in bioinformatics and omics research. Developing bioinformatics at universities needs further professorships to be established. Consideration needs to be given to strong interdisciplinarity when filling such professorships, and systems biology-driven bioinformatics should be promoted in particular. In medicine the improvement of interdisciplinary career profiles is vital so that young talent has a place in the system and does not, as is frequently observed, migrate abroad. Omics technologies and the associated infrastructures benefit from innovations that are developed across disciplines. For this reason it should be made more attractive for talented researchers to transfer, for example, from physics and informatics into life sciences and vice versa. Also advanced training should be simplified. In order to do this, subject boundaries in teaching, research and knowledge transfer need to be overcome.

Recommendations

Life sciences belong to the leading disciplines of the 21st century. The use of omics technologies is taking research in life sciences and understanding of biological processes to a new level. In light of the presented observations and analyses, the *Report on Tomorrow's Science* gives the following recommendations:

1. Research in the life sciences in Germany can only remain internationally competitive by strategically setting up a national omics and IT infrastructure. To this end, a nationwide network of distributed centres should preferably be created, enabling research, education and the rapid translation of new findings based on current state-of-the-art technologies. The network should be managed by an inter-institutionally set-up coordination committee.

2. Universities and non-university institutions participating in the network should be linked more closely via the infrastructure to facilitate access to the new technologies for researchers and students, to integrate technology centres more heavily in education and training and to bundle specialist expertise in interdisciplinary research projects. In order to avoid losses of expertise and guarantee appropriate capacity utilisation of existing equipment, an efficient use of personnel and technical resources must be a priority.

3. Adequate storage, evaluation and transfer of omics data urgently require a massive expansion of the IT and bioinformatics infrastructure both at non-university centres and at universities in Germany. Within the infrastructure, binding standards for data collection, processing, quality control and storage should be developed collectively. The standards should preferably also be adapted at the European and international level.

4. The funding of the organisation entrusted with this long-term task of coordinating and further developing the omics and IT infrastructure in Germany, must be secured by federal funds in a sustainable way.

5. Training in life sciences should place emphases on omics technologies already at an early stage of the course of studies. Via the infrastructure with its technical excellence, training could be structured more efficiently across institutions and federal states and new training models could be developed.

6. To cover the personnel requirement for omics research and the associated bioinformatics, it is essential to design the corresponding career paths more transparently and diversely. In addition, new incentives for IT infrastructure development are necessary.

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The genesis of *the Report on Tomorrow's Science*

The publication series *Report on Tomorrow's Science* is produced on behalf of Leopoldina for science-based advice to policymakers and society. These reports incorporate topically systemic potentials and challenges of science development in Germany.

In October 2010 the Presidium of Leopoldina suggested setting up a working group to react to the challenges of science development and the corresponding call for action. Consequently, in 2011 the Scientific Committee *Report on Tomorrow's Science* picked up a topic that had been previously discussed in the Scientific Committee *Life sciences*: the development of the science system using the example of omics technologies.

To assess the present use of omics technologies in life sciences research and teaching, the state of development and the accessibility of infrastructures beyond their own experience, the Scientific Committee conducted four expert discussions between 2012 and 2013 with representatives from non-university research and research funding organisations, from universities and from the Federal Ministry of Education and Research (BMBF). In the expert discussions, experiences with life sciences research infrastructures abroad and constitutional aspects of financing university and non-university infrastructures were also discussed. In addition, in 2013 a nationwide survey was carried out of all life sciences including medical faculties on omics technologies in teaching, research and infrastructures. Between March 2012 and December 2013 the Committee drafted the *Report on Tomorrow's Science*. This draft was reviewed in February 2014 by eight experts from Germany and abroad. The final draft takes into consideration the experts' comments and their suggested amendments.

The first *Report on Tomorrow's Science* by Leopoldina entitled *Life sciences in transition – Challenges of omics technologies for Germany's infrastructure in research and teaching* was adopted by the Leopoldina Presidium on 21 May 2014.

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