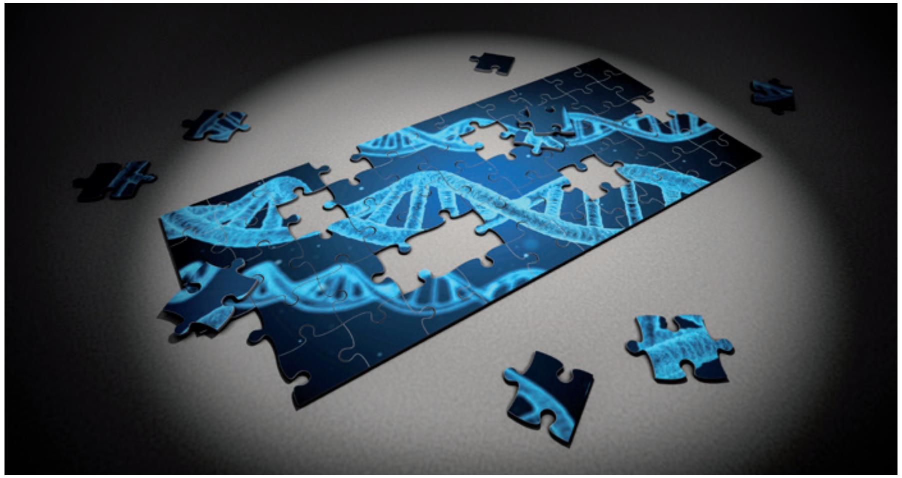
DECHEMA

POSITION PAPER

Taking biotech research to the next level

Miniaturization, automation and digitization are revolutionizing laboratories and the development of biotechnological processes and products

Contents



I. Introduction

Digitalization and its consequences for industry and society are currently being widely discussed - not only in the context of the revolutionary developments in „Industry 4.0“. In biotechnology in particular, converging developments are under way, driven by new tools from the fields of miniaturization, automation and digitalization. By the term „digitalization“ we mean here the comprehensive virtualization of the development of products and process steps through to the operation of biotechnological production processes. The resulting digital images of resources, procedures and processes are often referred to as „digital twins“. They are linked to their real counterparts in both directions and thus implement a bidirectional flow of information. This results in completely new possibilities, e.g. for information acquisition, product development and control of processes.

This position paper that has been introduced in 2018 and is now available in an updated English version focuses on the disruptive potential of digitization, automation and miniaturization in research and development of biotechnological processes, especially in the field of strain and bioprocess development. In scale-up and industrial production monitoring, digitization is also highly relevant and promises significant progress for these areas. However, these issues are largely similar to those that also apply to chemical processes. They are therefore not the subject of this paper, but have been discussed for example by the temporary working group „100% Digital“ (for more information see dechema.de).

Automation and digitalization are terms not usually associated with the biotechnology industry, but which have nevertheless played an increasingly important role in recent times. However, the real driving force behind current developments in biotechnological strain and process development is first and foremost miniaturization, because it leads to a multiplication of experimental and analytical throughput. This requires automation in order to guarantee the higher throughput in miniature format, and then almost inevitably entails digitization in order to be able to provide high-quality and informative data quickly.

This is not about the incremental improvement of existing products and methods, but rather about the potential for a disruptive change that will radically alter existing approaches in biotechnology. Awareness of such a technological upheaval opens up great opportunities and, at the same time, risks for the industry. In biotechnology in particular, groundbreaking developments are currently taking place at various locations that will converge in the medium term and fundamentally change workflows, processes and business models. This is especially true for industrial development processes. This paper would like to draw attention to this and point out new paths

II. Relevant factors

A large number of individual developments is currently taking place in biotechnology. In the near future, their convergence will have similarly serious consequences for an entire industry as have been experienced by the manufacturing industry. Consistent miniaturization, automation and digitalization will shorten development and production cycles and lead to significantly greater flexibility and diversity of products:

- The development of new production organisms in industrial biotechnology can now be automated to such an extent that over 10,000 genetically modified strains can be specifically generated in just one week and also tested automatically. Parallel developments in the field of enzyme development already reach similarly high throughputs.
- The concepts of synthetic biology are currently revolutionizing the approach to biotechnology. Through the consistent application of modularization and building block concepts, biological systems are being opened up for an engineering approach. Modular biological systems fit perfectly into digitalization concepts. The automation of all development steps for an industrial production process will be the logical consequence.
- With the “Global Biofoundry Alliance”, a network of facilities for the automated development and optimization of strains and processes for biotechnology has been established worldwide. The establishment of publicly funded facilities is made significantly easier by the availability of inexpensive open source laboratory robots.
- Modern laboratory assistance systems using augmented reality methods will interlink human laboratory work with digital systems to an unprecedented extent, leading to a significant increase in productivity.
- The ongoing miniaturization of biochemical analytics, particularly in systems biology “omics” methods, will enable development steps to be carried out with ever higher throughput in a smaller space. Today, gene sequencing is already possible on a USB stick-based device. Novel acoustic liquid handling technologies already enable the analysis of nanoliter sample volumes in high throughput.
- In the medical field, automated laboratories now allow the production of induced pluripotent stem cells to develop patient- or organ-specific cell systems for drug screening and therapy.
- High-throughput platforms for the cell-free expression of proteins allow the screening of huge libraries of plant and membrane proteins, some of which are difficult to express, with very short cycle times.
- An analogous development is taking place in the cultivation of microorganisms. Today, microcultivation systems in combination with laboratory robotics achieve comparable results to bioreactors on the laboratory scale. With today’s microfluidic systems, the next miniaturization step is already in the pipeline.
- “Smart” software systems can enable largely automated execution of development processes by using artificial

intelligence methods and can be integrated into decision support systems.

- The stream of information produced by miniaturized analytical systems is increasingly confronting modern biotechnology with the problem of evaluating large volumes of data (“big data”) in the development of new products. Bioinformatic methods from the field of machine learning to “smart data” are already an integral part of many working environments.

- “Continuous Bioprocessing” opens up new avenues for the production of a variety of small-volume, but often extremely high-priced products in small-scale modular plants. Production units are flexibly combined to build process chains and thus resources are used for several processes simultaneously. This is inconceivable without end-to-end digitalization.

- The traditional strict separation of laboratory development and production process will also be overcome more and more in industry. Production process data will soon be digitally available and usable at any time in the same way as laboratory data, thus enabling continuous integrated improvement and further development of production processes already in operation.

- An important pillar for the operation of biological production processes is represented by on-line sensor systems for the essential biochemical parameters, which are often not selectively accessible. Today, large amounts of data are generated by indirect measurement methods, from which, in combination with intelligent evaluation algorithms, relevant system information can be obtained.

- Sensor systems are increasingly doing more than just providing valid data. They are becoming more intelligent in the sense of extensive self-monitoring and self-diagnosis capabilities, integrated data evaluation with logic and control functionality, or interactive networking with other components in the process environment.

III. The next generation of processes and products

Combined, these pieces of the puzzle create a picture of a biotechnology industry in which the way new products are developed and efficient manufacturing processes are designed will change dramatically. This will result in new markets and changed business models. The first companies - especially in the USA - have already adopted the new concepts and are increasingly building on miniaturization, automation and digitalization. Examples include Amyris, Zymergen, Ginko Bioworks, Genomatica and Conagen in the U.S. and Boehringer Ingelheim, Roche and GeneArt in Germany.

In the medical field, automated high-throughput analytics are indispensable, as the Corona pandemic impressively demonstrated. Due to the required enormous initial investments German start-ups need the support of research institutions. At the same time, several German biofoundries are being established at research institutions.

The biotechnological product and process development of the future will systematically combine all available resources within the framework of flexible, digitally supported workflows. The industrial development pipeline of the future will thus resemble an automated production line in the automotive industry rather than a classic laboratory operation. The employees in the laboratory will be able to concentrate on the essentials thanks to assistance systems and will work predominantly at the computer, where they will design biological systems and processes on the drawing board, commission AI-supported experiments using distributed resources, and monitor automated, modular production processes with intelligent sensor networks.

These developments will have considerable consequences for the design of the working world, resulting in completely new requirements for company and academic training. While the implementation so far is still limited to a few academic working groups and industrial laboratories and mostly concerns individual aspects, it is nevertheless foreseeable that the potential of these technologies can only be fully exploited when they are combined.

IV. The challenge of bioprocess development

One of the central challenges in the development of new biotechnological methods, processes and products are the excessively long and thus difficult-to-calculate development times and the associated economic uncertainties. In contrast to process and product development with classical technologies, biotechnology is particularly confronted with the problem of poor predictability: against the background of volatile markets, the feasibility, productivity and competitiveness of a process can only be estimated over a very short time horizon. In the context of a sustainable bioeconomy, there are also considerably increased demands on the flexibility of processes with regard to the raw material base. Similarly, the requirements with regard to the adaptability of the product range are increasing, e.g. in the context of personalized medicine. New biotechnological developments are thus associated with high scientific and economic risks. As a result, industrial companies are still reluctant to develop new biotechnological processes and products.

This is precisely where the new concepts of miniaturization, automation and digitalization in biotechnology come in. In some cases, development processes can already be accelerated considerably through the consistent application of high-throughput methods in conjunction with bioinformatics algorithms and machine learning. However, the technical possibilities are far from exhausted. One key to success is miniaturization down to the dimensions of single cells and molecules in combination with high-resolution analytics and massively parallel experiments for the required increase in throughput. In addition, enormous synergy effects can be expected through tool integration. While many breakthroughs in recent years (e.g. in the field of gene sequencing and synthesis) are already based on miniaturization, the potential of microsystems technology in biotechnology is far from being exhausted. These include, for example, microreactors, microfluidic systems, micro-sensors or miniaturized analytical systems.

Especially in the field of bioprocess development, large discrete and contiguous parameter spaces have to be sampled. This concerns the selection of suitable strains on the one hand and the process conditions (culture medium, temperature, pH, feeding profile, etc.) on the other. The next stage of development in this area will be (semi-)automatic experimentation: intelligent algorithms determine the performance indicators (growth rates, yields, space-time yields, etc.) required for process assessment fully automatically, initiate the necessary experiments and perform parameter optimization. In the process, the often high measurement inaccuracies in miniaturized experiments must be included in the experimental design.

Humans will still be able to make controlling decisions in such systems, advised by information condensed to the essentials as calculated by the system. Such information compression will become more and more important in the future, because the automatically generated flood of information based on large amounts of data can no longer be handled. Work is already underway to accelerate standard -omics analysis methods (transcriptomics, proteomics, metabolomics) to keep pace with data generation. The single-cell video data obtained from at-line microscopy systems provide even more data, which must be reduced to the relevant information (e.g. cell morphology, fluorescence) in real time.

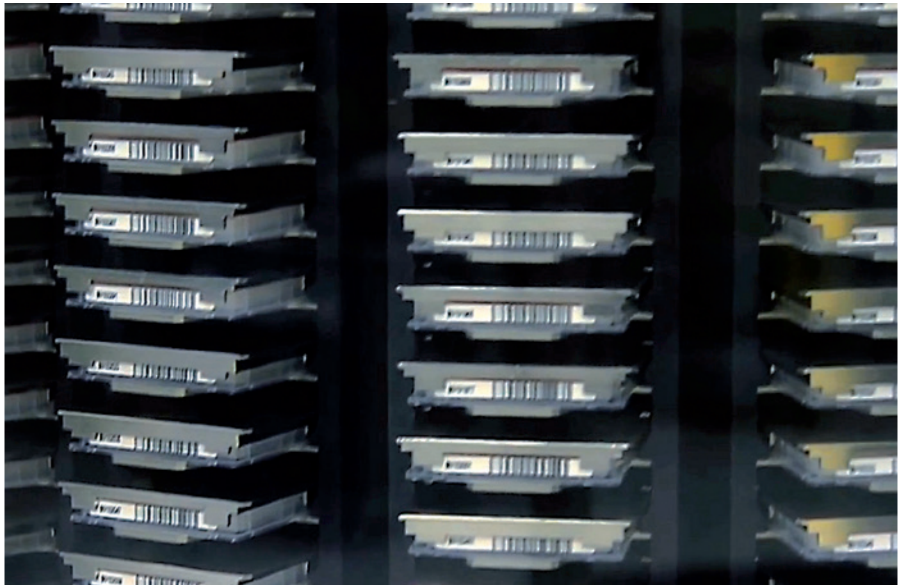
V. The role of humans

Fully autonomous experimental systems with a high degree of automation for strain and process development in biotechnology do not aim to completely replace humans. Nevertheless, the role of humans in the biotechnology industry of the future will change dramatically. The paradigm shift will be that humans are currently only supported by isolated highly integrated automation systems (such as pipetting devices or microcultivation systems) in the laboratory. In an automated laboratory of the future, the automation system will take over all elementary laboratory tasks, and humans will primarily play the role of final information assessor and process decision maker.

The time spent in the laboratory could be limited to the development and establishment of new methods, the assurance of experimental quality and processes, and technical maintenance work. The daily work of the biotechnologist thus changes radically. Humans in the laboratory must adapt to the automated processes. Modern methods of human-machine communication in conjunction with augmented reality technology, such as data glasses, will facilitate work in such complex overall processes or even make it possible in the first place and lead to considerable increases in productivity.

At the same time, work will increasingly shift to the computer workstation, a trend that can also be seen in other industries. The use of constantly improving algorithms for protein structure prediction, metabolic pathway design, or digital twins for process development will continue to increase. The ability to design experiments and analyze complex data sets will be increasingly in demand. In order to make well-founded decisions, humans will depend on the support of information systems, statistical methods and artificial intelligence in conjunction with visualization methods that are optimally tailored to human perceptual abilities.

VI. Technical fields of action



Miniaturization: Miniaturization is the main driving force behind the current transformation. The drive for further miniaturization and the use of new physical principles in combination with a drastically increased throughput continues, especially in basic life science research. However, this does not necessarily result in systems that are superior to existing solutions. In many cases, miniaturized systems are initially more prone to error and exhibit lower reproducibility than their classical antetypes. This is the reason why the full potential of miniaturization can only be exploited through parallelization and automation. This is particularly true for the inclusion of -omics analytics, which must be accelerated and operated at high throughput and made compatible with automation systems. Further challenges arise from the required physical and digital interfaces. This is demonstrated, for example, by the coupling of microfluidic chips or the handling of extremely small sample quantities in the field of mass spectrometry. Furthermore, a wide range of opportunities will arise in this field through the use of modern 3D manufacturing systems, which can already print structures in the submicrometer range.

Modularization of biological systems: Synthetic biology also continues to be highly dynamic as another driving force of development. It is the inherent idea of modularization that is driving developments. However, the same applies here as in the case of miniaturization: only concepts that keep an eye on industrial feasibility - especially in the context of automation systems - will be useful in the long term. The combination of synthetic biology with laboratory robotics can therefore currently be observed in many places.

Device standards: Especially in the area of miniaturized laboratory devices, completely new requirements are arising in the context of digitalization. Whereas such devices have so far mostly been operated in “stand-alone” mode by laboratory staff, in the future they will have to be able to be integrated into automated processes and thus be compatible with other devices. The much-cited “Internet of Things” is already charting this course. While the technical coupling of devices via the Internet is now standard, the development of suitable protocols for standardized communication remains a challenge, particularly in the laboratory sector. Two standardization consortia focused on laboratory automation are working in this direction: SILA 2 and LADS. However, there is also already the universal OpenAPI standard supported by all major IT groups. In the end, the market will decide.

Laboratory robotics: The robotics required to automate biotechnological development processes is available today. However, new challenges arise when partially automated devices, such as microcultivation equipment, have to be integrated into robot-assisted experimentation systems to perform fully automated experiments. The coupling of different laboratory robots to robotic systems in analogy to automobile manufacturing is also already in full swing, although currently still delayed due to integration problems.

Human-machine systems: Humans will continue to perform tasks in the context of automated experimental systems, but they must be able to communicate seamlessly, meaningfully, and in a standards-compliant manner with an automation system. The human operator must be able to gain a complete overview of the current state of the development process currently being worked on at any point in time. Modern data science provides algorithms to extract information essential for human decision-making from large amounts of data. New methods for human-machine communication are also currently being developed under the term “laboratory of the future”. In this context, laboratory assistance is increasingly relying on augmented reality methods.

Information infrastructure: Data management - from cultivation data to data from mass spectroscopy and high-throughput sequencing - is an essential prerequisite for virtualization and thus digitization, starting with the electronic laboratory notebook. This also includes the unique identification of all biological systems used, experiments performed or samples obtained from them. For this, consistent data formats must be created at all levels. The highly distributed generation of data also requires new infrastructures that can e.g. be based on modern cloud solutions. Scalability will also become a central requirement. In the long run, the management of laboratory data and process data will merge. Traditional laboratory information and management systems (LIMS) are still unable to cope with this.

Overall process control: Today, the automation of entire production lines in industry involves conceptually mature process control systems that organize the overall process at various levels of abstraction. Comparable systems are not yet known in the field of strain and process development for biotechnology. However, from an abstract point of view, experimental processes are often more similar to business processes than manufacturing processes. In this context, flexibly configurable, fault-tolerant and nevertheless standardized workflows gain great importance. Algorithms for scheduling, i.e. sequence coordination, are becoming increasingly important for optimal resource utilization.

Experiment planning and data analysis: Ultimately, the planning of goal-oriented experiments based on large amounts of data is the most important task for humans in the automated experiment system. In this context, huge volumes of raw data, such as mass spectra or microscopic video sequences, must first be automatically preprocessed into useful data. The heterogeneity of the large data sets generated in this way poses a challenge for statistics and artificial intelligence methods, such as multivariate analyses, time series analyses, data mining or machine learning. Classical experimental design methods also quickly reach their limits when correlations are highly non-linear or the prevailing experimental parallel approaches require new strategies. In order to implement the vision of automatic experimentation, all of these prerequisites must be met.

VII. Further fields of action

The examples of miniaturization, automation and digitization mentioned above all touch on the subject area “biotechnology research”, but they are not taking place in a coordinated manner, nor are they perceived as a coherent phenomenon. The potential and extent of the changes are currently not fully recognized. For Germany as a traditionally engineering-oriented country, the convergence of these technologies offers special opportunities that should definitely be exploited.

Important fields of action in this context are:

- **Observation, monitoring and systematization** of the developments taking place, e.g. through market overviews, white papers and information/discussion events.

- **Networking of the stakeholders** in order to counteract the emergence of diverse isolated solutions and resource-consuming parallel developments.

- **Fundamentals of miniaturization:** research into new approaches to miniaturization of analytics (methods, apparatus) as well as microscale experimental systems should be further promoted as a driver of development.

- **Virtualization ("digital twins") of workflows and processes** to integrate technologies, geared both to the interlinked operation of devices and to the broader networking of the entire research, development and production chain is critical to success.

- **Integration of technologies by creating demonstrators and platforms** to develop showcases for the new technologies, to accelerate research, but also to promote further development of the technology.

- **Smart algorithms, sensors and software systems** that are able to autonomously recognize environmental contexts and make decisions about how to proceed with a step or experiment.

- **Interface standards** to promote the convergence of a wide range of technologies. The development of corresponding standards should be critically accompanied and tested by means of test scenarios (benchmarks).

- **Market innovations:** Digitization makes alternative business models possible. Areas such as the bioeconomy or personalized medicine will benefit from this, but will also create new boundary conditions. The economic consequences must be thought through.

- **Accompanying social research:** The expected changes will have consequences for the world of work and society that are not yet foreseeable, because on the one hand automation will require new skills and on the other hand the end consumer will be able to use new products. The participation of the relevant social groups is necessary.

- **Education:** Miniaturized platform technologies must be made available at universities in intelligently networked laboratory environments at the latest state of development in order to enable them to fulfill their central role in research and academic education of appropriately qualified specialists.

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