



Fraunhofer
IPT

Trend report

Laboratory 4.0 – Next Generation Production in Life Sciences

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The laboratory of the future

Production landscape in life sciences

Despite their different disciplines, the life sciences share the common goal of improving environments, processes or products that are in direct contact with living organisms. The wide range of topics is accompanied by very different scientific and technical challenges. Accordingly, the state of the art in terms of production technologies also varies greatly. This reflects several criteria such as scalability, degree of digitalization, reproducibility and sustainability.

In the chemical industry or in the manufacture of some medical technology products, production facilities are often very advanced and already follow many approaches that can now be assigned to the term "Industry 4.0". The disciplines that are more closely related to biology are often further behind in terms of the degree of industrialization. Reasons for this are:

- Biological variability
- Personalization/individualization
- Complexity and time-sensitivity of manufacturing processes
- Degree of novelty and innovation of the products
- Quality standards and regulatory hurdles

Consequently, the production processes for biological or bio-hybrid products are often still very manual. Many products are therefore manufactured permanently in the laboratory and not in a dedicated production environment. On the one hand, this has the advantage that production in the laboratory is more flexible and adaptable, but on the other hand it is difficult to achieve high throughputs without extensively increasing workload at the same time. The following section outlines the vision of a biotechnological production laboratory that combines the advantages of both sides.

Vision of a Laboratory 4.0

The following case study illustrates the current challenges in bioproduction laboratories:

A biopharmaceutical company produces a product consisting of living cells for therapeutic use. The challenges in production are:

1. the cultivation of the cells is accompanied by a large variance (fluctuations of +/- 30 % in the cell yield)
2. production consists of many complex and time-consuming processes
3. each product must be modified and dosed individually for each patient
4. regular 100 % quality controls are necessary

5. there are high purity requirements
6. all process data must be documented precisely and in detail.

Established, commercially available production systems that can be used for automated, resilient and sustainable production under these conditions are very limited. According to the current state of the art, such products are manufactured in GMP (Good Manufacturing Practice) clean room laboratories with a high level of manual labor. Occasionally, semi-automated solutions are implemented for individual process steps, such as a pipetting robot to carry out liquid handling processes automatically or a digital lab book to document process data in a structured and faster way.

A production laboratory, as it is widely used in the biopharmaceutical industry, is characterized by the following features:

- There are multiple workstations where work is done manually
- SOPs (Standard Operating Procedures) are displayed digitally
- Data is entered in a digital lab book
- Repetitive liquid handling tasks are performed by a pipetting robot
- Quality controls, e.g. using microscopy, are carried out manually and evaluated manually
- Material is transported manually
- Products are packaged and stored semi-automatically

The vision of the laboratory of the future brings modern "Industry 4.0" approaches into this scenario.

The "Laboratory 4.0" has the following characteristics:

- There is a fully automated isolated platform. No personnel are required at the product. All laboratory processes can be fully automated or controlled remotely.
- SOPs are transferred to the production platform's control software and are processed automatically.
- All process data is tracked and monitored live.

- Quality controls are carried out automatically and efficiently using high-speed microscopy. At the same time, the recorded data is evaluated using artificial intelligence and the next process steps are determined automatically.
- All material transport is robotic. Staff only have to remove finished products.
- Used waste materials are automatically sorted in advance and prepared for reprocessing.

The transition from manual biolabs to digitized and automated cleanroom production environments for highly regulated products has not yet been established fully in all areas of the biopharma industry. However, some key technologies are already available and established in other industries, while other technologies are still in the research and development phase. Some of the enabling technologies for the transformation to "Laboratory 4.0" are listed below and explained in more detail in the following chapters.



Figure 1: Visualization of the "Lab4.0" based on the real automation platform "StemCellDiscovery" at the Fraunhofer IPT

Enabling technologies

The fundamental building block of a modern production environment is digitalization. Only by networking all laboratory equipment, computers and robotic systems automation and increasing efficiency are made possible, which in turn creates the basis for sustainable and resilient production. The Fraunhofer IPT is conducting intensive research into digitalization topics - both in terms of networking and in the areas of control technology and data management using artificial intelligence (AI). The following figure shows digitalization with its individual areas as a key enabler for automated, sustainable and resilient production.

One result of years of research that has established itself in the field of laboratory automation is the software COPE. It enables the networking of laboratory equipment from a wide range of manufacturers and the connection of machines, such as industrial robots, and forms a central user interface for controlling a fully automated platform.

AI is becoming increasingly important and is also becoming more and more popular in production environments for efficient data management. In the biomedical context, however, the use of AI should be approached with caution, as AI systems often act as a “black box” and the output of results is not always transparent. This is particularly critical when it comes to handling patient data. The Fraunhofer IPT is therefore working on topics such as “Trustworthy AI” in order to enable AI applications within a secure and regulatory-compliant framework.

Another key technology for efficient production laboratories is the integration of modern metrology and analytical systems that create a solid database for intelligent evaluations. Among other topics, the Fraunhofer IPT is working on three innovative technologies that are particularly relevant for the biological sector:

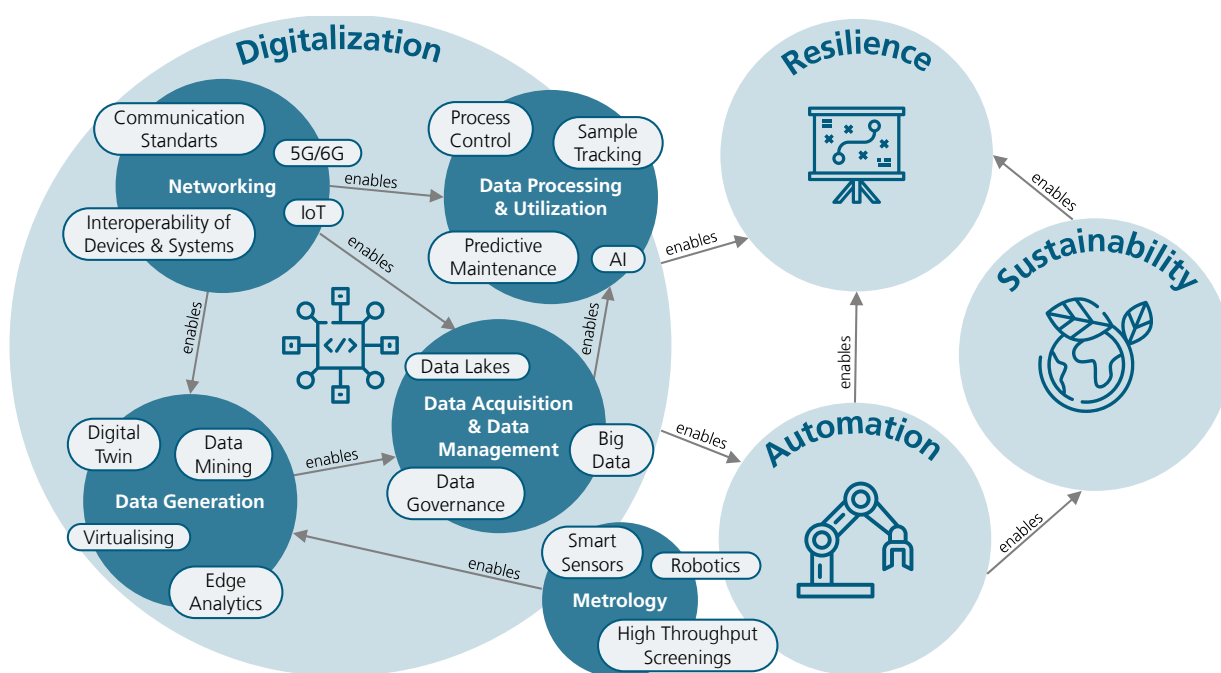


Figure 2: Digitalization as a key enabler for resilient and sustainable production labs

1. High-speed microscopy (HSM): This technology enables the high-throughput analysis of samples, for example for screening applications or 100 % quality control of products. HSM technology offers considerable advantages in terms of speed and precision.
 2. Optical coherence tomography (OCT): This technology makes it possible to examine biological samples non-invasively, i.e. contact-free and without harmful radiation, in three dimensions and thus, for example, to evaluate tissue structures.
 3. Microfluidics-based analytics: This method opens up a broad spectrum of innovative possibilities for detecting special substances such as viruses. The Fraunhofer IPT has already developed various lab-on-chip and lab-on-disc devices.
- Manual production: In the clean room, work steps such as pipetting processes and microscopic quality controls are carried out by appropriately equipped personnel on open vessels.
 - Semi-automated production: Here, work is largely carried out in closed systems so that the cells are not exposed to the environment. Individual process steps can already be partially automated using various laboratory devices. This means that fewer personnel are required and the risk of contamination is lower.
 - Fully automated production: This stage requires no personnel for the individual process steps. The original cell samples are introduced into the system and the finished cell products are removed at the end. All quality controls and data acquisition are automated.

Diese Technologien schaffen die Grundlagen, um bisher manuell betriebene Biolabore zu automatisieren.

These technologies are important enablers for realizing the automation of manual laboratories. The Fraunhofer IPT has already successfully implemented numerous automation projects. Figure 3 shows the three stages of the degree of automation using the example of CAR-T cell production:

One of the major challenges for the biopharmaceutical industry and the laboratory of the future is to make all processes sustainable and climate-neutral. However, approaches to reducing the ecological footprint are encountering difficulties in bioproduction, as energy-intensive processes and disposable items are still standard. This is mainly due to the high purity standards and regulatory requirements.

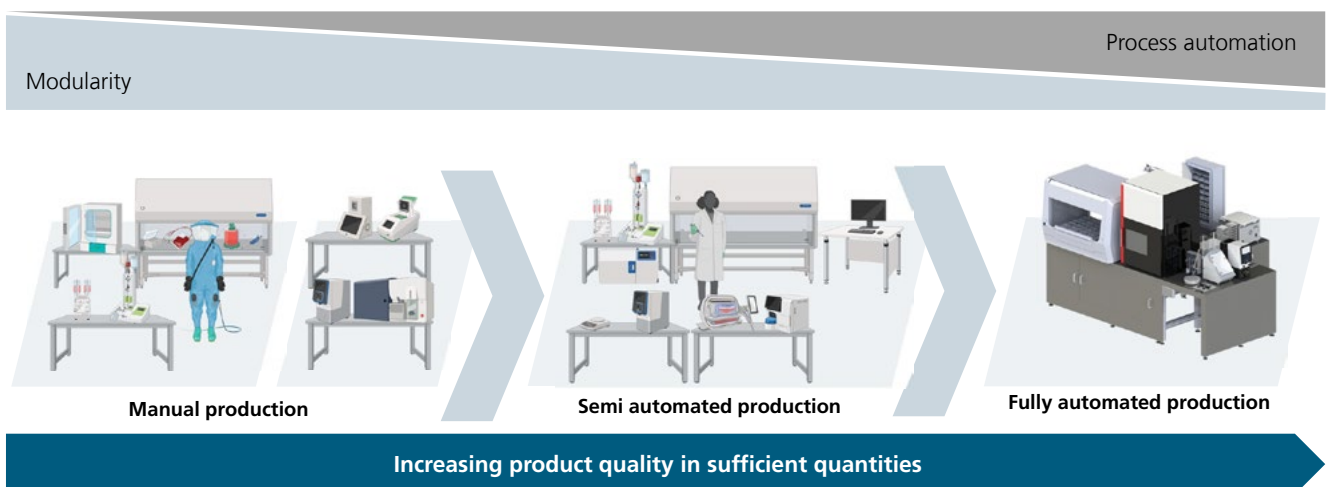


Figure 3: Three stages of production laboratories with increasing levels of automation using the example of CAR-T cell production

Digitalization as a foundation

Fully networked laboratories

What is state of the art in digitalization and networking in laboratories?

The importance of digitalization and networking in the laboratory is constantly increasing in the life sciences industry. Thanks to modern technologies, it is possible to link devices with each other, exchange data and automate work flows. Comprehensive networking enables more efficient monitoring and control of laboratory processes. It also contributes to increased data integrity, which in turn ensures greater transparency and traceability and enables consistent quality assurance. Digitalization and networking offer considerable potential for innovative solutions that drive progress in research and development and accelerate production [1, 2]. However, laboratories are currently

facing considerable challenges. Most laboratories have a wide range of equipment from different manufacturers, which can only be harmonized to a limited extent by electronic support. Merging and contextualizing the generated data is therefore complicated, error-prone and time-consuming. As a result, a large number of laboratory activities are currently still carried out manually. Instead of integrating the data electronically, the transfer of results and measurement data from the devices to systems is carried out manually. However, as the frequency of these manual steps increases, so does the likelihood of errors in the data [1, 2]. But how can laboratory networking and data exchange between laboratories, individual devices and existing software solutions be implemented in practice?

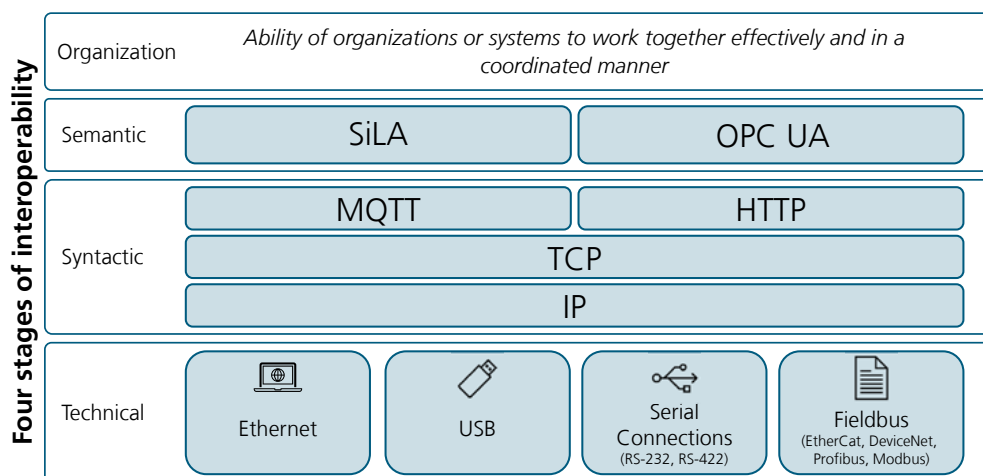


Figure 4: The four levels of interoperability. [1, 4]

There is no one-size-fits-all solution for the interoperability of systems and devices

A simple answer is that the hardware and software components used must be interoperable. In IT, interoperability describes the “degree to which two or more systems, products and components can exchange information and use the exchanged information”. [3] However, due to the variety of assets, products and systems used in the laboratory, this exchange of information is a real challenge. Interoperability can be divided into four successive stages, which are shown together with the most important interfaces and communication protocols in Figure 4. [1, 4]

Physical interfaces, such as USB and Ethernet, enable pure data exchange without knowledge of the format and meaning of the data (technical interoperability). If devices are syntactically interoperable, they exchange data in a commonly understood format (e.g. MQTT, HTTP). MQTT (Message Queue Telemetry Transport) is an open communication protocol that was developed for the exchange of data between machines (M2M) and is frequently used in the Internet of Things (IoT). It is based on the publish/subscribe principle and enables the reliable transmission of large amounts of data in a short time. [4, 5]

Data models and standardized terms are used to create semantic interoperability in which the devices can correctly interpret the meaning of the exchanged data. OPC UA and SiLA are more widely used protocols. OPC UA (Open Platform Communications Unified Architecture) is a platform-independent,

service-oriented architecture. In addition to various communication methods (publish/subscribe and server/client), OPC UA offers access to information models that have been specially developed for laboratory applications and provide basic data exchange schemes in the laboratory sector. [4, 6]. SiLA (Standardization in Lab Automation) is an open, standardized interface specifically for lab automation and is based on client-server communication. It enables device control, data exchange and the management of status messages. SiLA enables laboratory devices and software systems to provide their services in a network. The SiLA features of a device can be described semantically and include the description, properties, commands, parameters and feedback values. [7] The final stage - organizational interoperability - enables data exchange in accordance with business rules (e.g. access rights). Despite various approaches, there is still no global standard in the laboratory sector that has been able to establish itself. Existing interfaces are very specific, sometimes not certified or without modern security features.

All in all, the laboratory sector still lacks a standard that has been able to establish itself worldwide. The existing approaches are often very specific and in some cases not certified or security-oriented. They focus more on data exchange than on the control of laboratory equipment. This limits their scope of application.

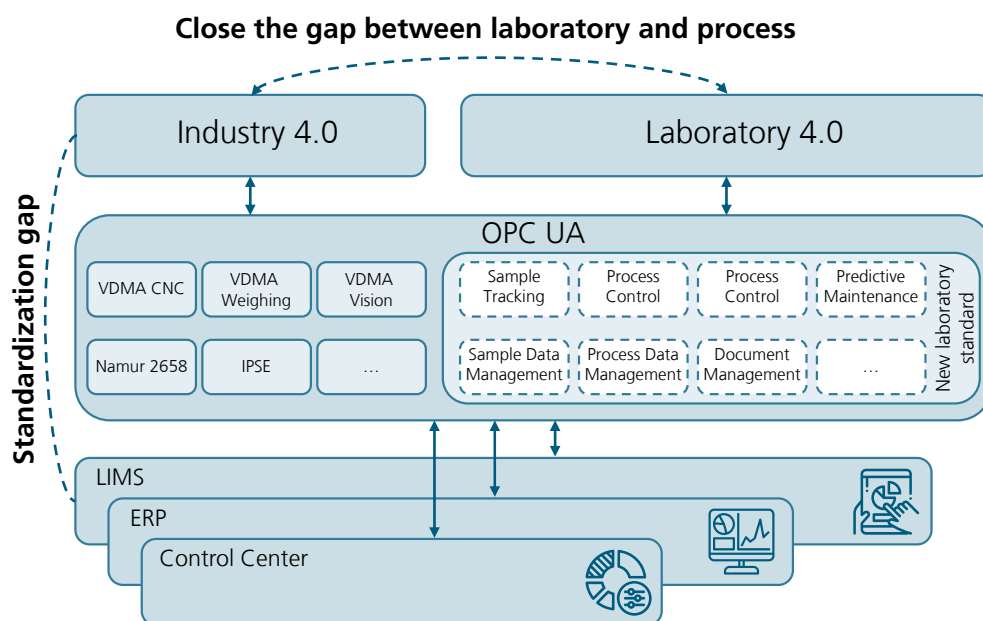


Figure 5: Integration of the new standard into an existing laboratory environment. [cf. 9]

OPC LADS: a new communication standard for the networked laboratory

Beginning of 2024 a new communication standard was published: The Laboratory and Analytical Device Standard (LADS) [8]. Companies from the German industry association for laboratory and analytical devices have joined forces with users to develop this new standard. [9] LADS is based on OPC UA and thus builds on technologies and standards from other industries that have already been tried and tested over many years, offering many advantages for use in the laboratory::

- OPC UA: manufacturer-independent and proven industry standard
- Platform independence at software and hardware level
- Security-by-design
- Plug-and-play interoperability of laboratory and analysis devices
- Coverage of a wide range of different laboratory and analysis devices thanks to device type-independent design principles

To date, LADS has primarily addressed use cases in the field of automation as well as service and plant management. The standard enables remote monitoring of the measurement of physical properties, the setting of alarms and the automated sending of notifications. Devices are controlled

by implementing functions that can be combined into more complex program sequences. Recorded data and results are then made available to the surrounding IT system for further processing. [8] LADS defines a series of properties such as device name, identifier, serial number, etc., which make the laboratory devices traceable for detection, management and maintenance tasks. The device status is monitored by recording operating times and maintenance intervals. Information on the device location is stored as geographical or organizational information in order to simplify maintenance and enable the use of autonomous robots and the tracking of problems in the long term. [8] Since the end of 2023, manufacturers and developers have been able to use the first reference implementations to test their own products and have them certified by the OPC Foundation. This brings consistent and independent networking between manufacturers, devices and systems within reach. Thanks to many years of experience in the digitalization and automation of laboratory equipment, the Fraunhofer IPT is able help companies implement their own reference implementation.

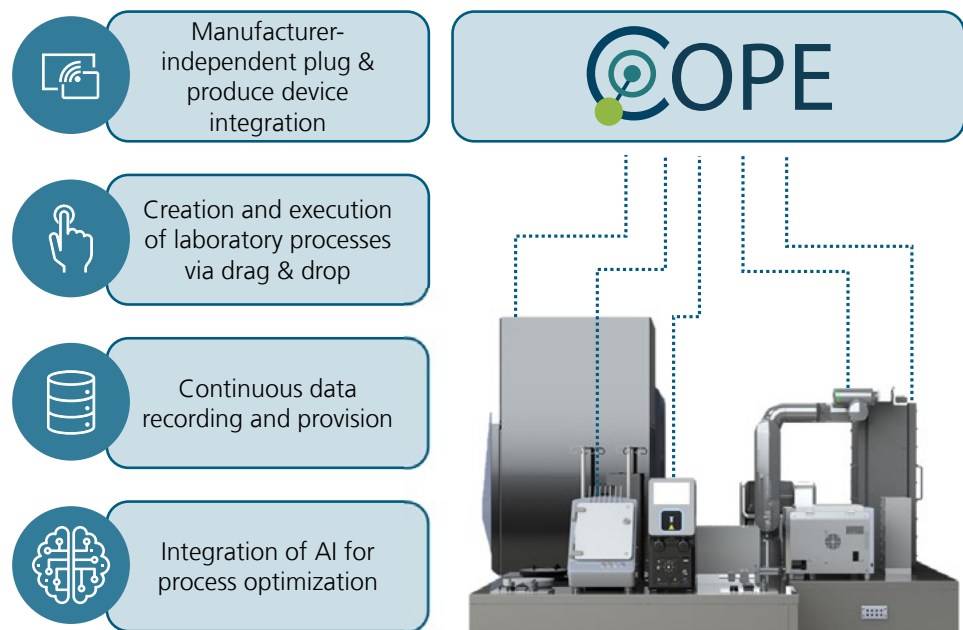


Figure 6: COPE as a central control system in the laboratory. [12]

The path to the digitalized laboratory together with the Fraunhofer IPT

Fraunhofer IPT has been working on digitalization and networking in the laboratory for over ten years. The focus is particularly on the central control and monitoring of flexible laboratory processes. To this end, Fraunhofer has developed the adaptive control software COPE (see Figure 6). COPE stands for Control, Optimize, Plan and Execute and describes the four key tasks of the software. COPE bridges the gap between information technology (IT) and operational technology (OT) by directly controlling laboratory equipment and executing processes (Execute), while at the same time recording and processing production data in order to plan and continuously optimize production processes. COPE and the interfaces and protocols described above enable the laboratory devices to provide their data and services in the network. This is made possible by the device-specific drivers (so-called cope.agents), which ensure interoperability and integrate the devices independently of the manufacturer using a plug-and-produce approach. Using a no-code environment, laboratory technicians can create and execute individual processes via drag and drop menu. Complex process chains can be created using IF branches and loops. All relevant data is recorded, processed and displayed in dashboards across all tasks. Processes and products are continuously improved through the integration of optimization algorithms and data analysis methods. [10, 11]

The Fraunhofer IPT is continuously improving COPE for customers and partners. In doing so, we focus on specific market requirements and implement the concepts of Industry 4.0 and IIoT in practice. Fraunhofer offers an ideal environment for the further development of the customized control software of the future.

The potential of artificial intelligence for the laboratory of the future

In order to leverage the potential of artificial intelligence (AI) in the laboratory of the future, a high-quality database is required as a starting point. According to ISO/IEC 25012, data quality can be divided into inherent and system-dependent data quality [13]. Inherent data quality refers to how well the data is suitable for depicting the facts under investigation, i.e. whether the data is consistent in itself or whether recorded data is complete. System-dependent data quality describes the extent to which a system is suitable for providing data for investigations, i.e. the availability of the system or how well data loss is prevented. In between, there are a number of other aspects of data quality that can be classified as inherent or system-dependent, such as the confidentiality or comprehensibility of the recorded data.

In addition to these criteria, metadata is a relevant aspect of laboratory data that is to be analyzed using AI. Metadata can be defined in different ways. One possibility is that metadata is the information we collect, store and share in order to describe things, interact with things and generate the knowledge we need from them [14]. Another perspective is that metadata is the sum of all the information you have about an information object [15]. Metadata is therefore the basis for traceable collaboration. After all, data can only create added value if everyone involved knows the content and context of the collected and analyzed data. Ontologies that define which objects exist, how they are to be described and how the relationships between the objects function are suitable for implementing all these aspects of data collection. However, new ontologies do not

have to be developed for every application. There are various institutions and databases that provide existing ontologies. [16, 17] With a high-quality database the potential of AI can be utilized. AI can be understood as the application of machine learning (ML) methods, with deep learning (DL) being a sub-category of ML [18].

AI applications for future laboratories

The major advantage of AI applications is their ability to process large volumes of data and discover complex correlations and patterns. Based on this, predictions for the future can be calculated. This results in a wide range of possible application scenarios in the laboratory of the future:

- AI applications are used to learn from large data sets and recognize patterns. This can be used in the analysis of genome data, drug development or the diagnosis of diseases.
- In laboratories, deep learning can be used to analyze medical images or predict drug activity, for example.
- AI-controlled robots can perform repetitive tasks in the laboratory, such as picking samples or carrying out assays. This increases the efficiency and accuracy of laboratory work.
- By using AI technologies, laboratories can create individual treatment plans based on a patient's genetic data. This enables customized and more precise medical care.

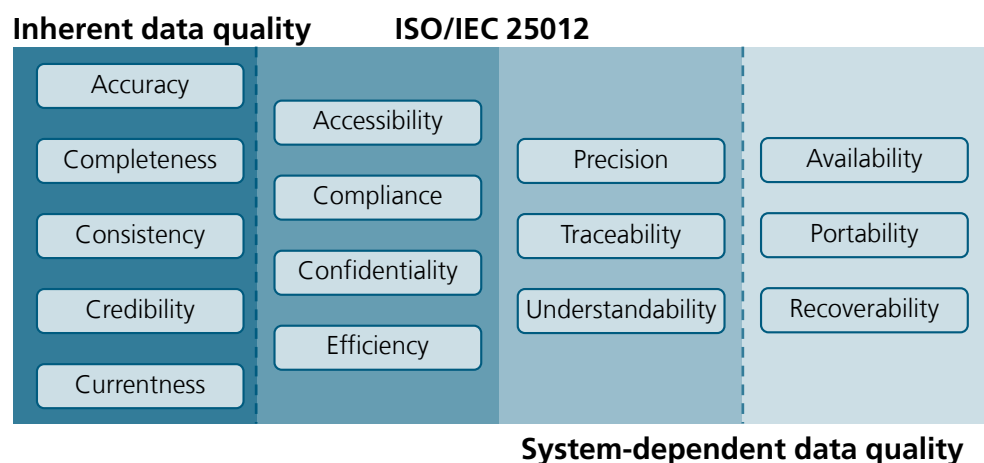


Figure 7: Division of data quality according to ISO/IEC 25012 into inherent and system-dependent data quality.

One of the particular challenges in the medical field is the high demand on the reliability and trustworthiness of such systems. Since AI applications contain data-driven stochastic models, classic software tests for deterministic software cannot guarantee these properties. An approach developed at the Fraunhofer IPT is suitable here, which quantifies trustworthiness when designing AI applications and provides methods to guarantee this during operation. The use case and the application to be developed are specified and then examined for risks. These risks can be mitigated or at least quantified using a collection of methods in the four dimensions of transparency, robustness, security and adaptivity [19, 20].

Along these four dimensions, the Fraunhofer IPT has gained experience in the development and operation of AI applications from which companies can benefit in a partnership. The successful development and use of AI applications offer various competitive advantages for modern laboratories. For example, complex correlations can be recognized more quickly, decisions by laboratory technicians can be supported by data and large amounts of data can be processed more efficiently.

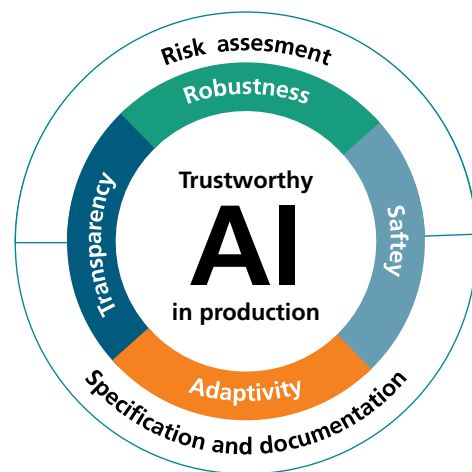


Figure 9: Division of the risk assesment into the four dimensions of transparency, robustness, security and adaptivity.

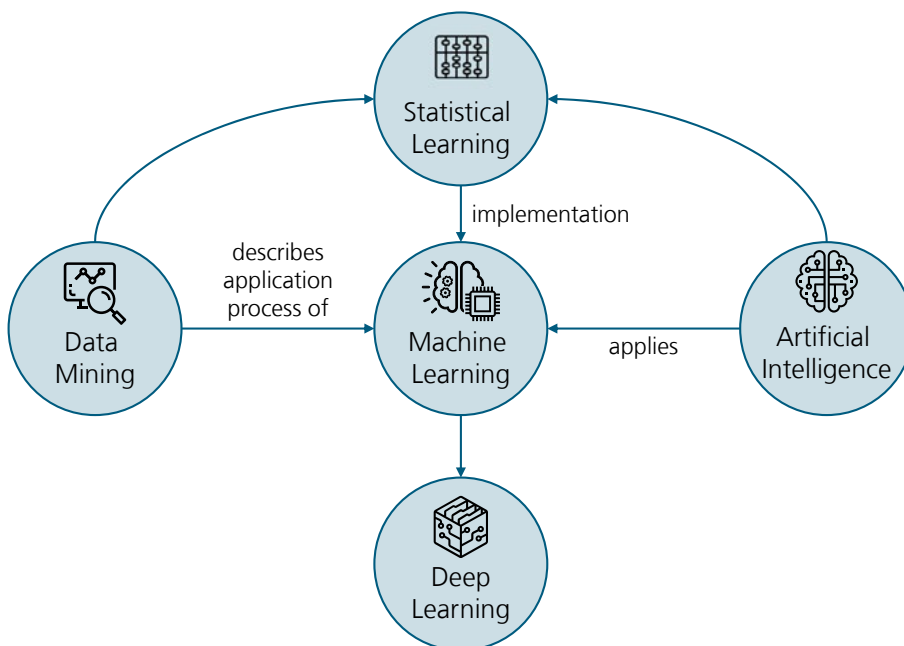


Figure 8: Various components for the composition of machine learning

Automation of laboratory processes

Laboratory automation to increase productivity

The production of biopharmaceuticals is often a highly complex and resource-intensive process that requires precise and reliable laboratory work. In consideration of increasing demands on quality, efficiency and throughput, laboratory automation is becoming increasingly important. By using automated technologies, modern biolabs can perform repetitive and time-consuming tasks faster and more accurately, leading to a significant increase in productivity. Automation enables greater reproducibility of results, minimizes human error and improves data accuracy, which is crucial for compliance with regulatory requirements. It also relieves staff and allows them to focus on more complex tasks, strengthening the company's ability to innovate. As manual production environments are still common today, laboratory automation offers a decisive competitive advantage and enables biopharmaceutical companies to work more efficiently and cost-effectively, which is particularly important in a highly competitive market sector.

The following figure illustrates qualitatively why it is advisable from a production technology perspective to introduce automation as early as possible in the product development process. In the early research and preclinical approval phase of the development of a new biopharmaceutical, manual operation is quite efficient and sensible. During the transition to clinical trials, the manufacturing process must be clearly defined and can only be changed later with a high regulatory effort. If the process has not yet been designed for automation up to this point, production must be operated manually in the long term. As more and more products are required as clinical trials progress, production capacities must also be increased. This means that new laboratories have to be equipped and additional specialist staff have to be hired or expensive manufacturing contracts have to be given to CDMOs. All of this leads to a reduction in production efficiency and the company symbolically goes through a "valley of tears". If semi-automated solutions are then established at a later date with great effort, production efficiency that comes close to a fully automated solution cannot be achieved in the long term.

Economic considerations of laboratory automation show that the installation of individual automation solutions, so-called automation islands, can save up to 17% of annual costs, even with the purchase of expensive equipment. This observation relates to a classic biolaboratory, in which new processes are frequently carried out and no standard operating procedures (SOPs) for the manufacture of a specific product need to be processed [21]. If the laboratory work is more focused on a production context and the aim is to manufacture a specific product as efficiently as possible according to a SOP, total laboratory automation makes economic sense. A cost analysis using the example of the production of human induced pluripotent stem cells (hiPSCs) has shown that when comparing manual and fully automated production, the total costs incurred could be reduced by around 40% over a period of 8 years [22]. This automation solution was implemented in the »StemCellFactory«, which is presented in more detail in the following chapter.

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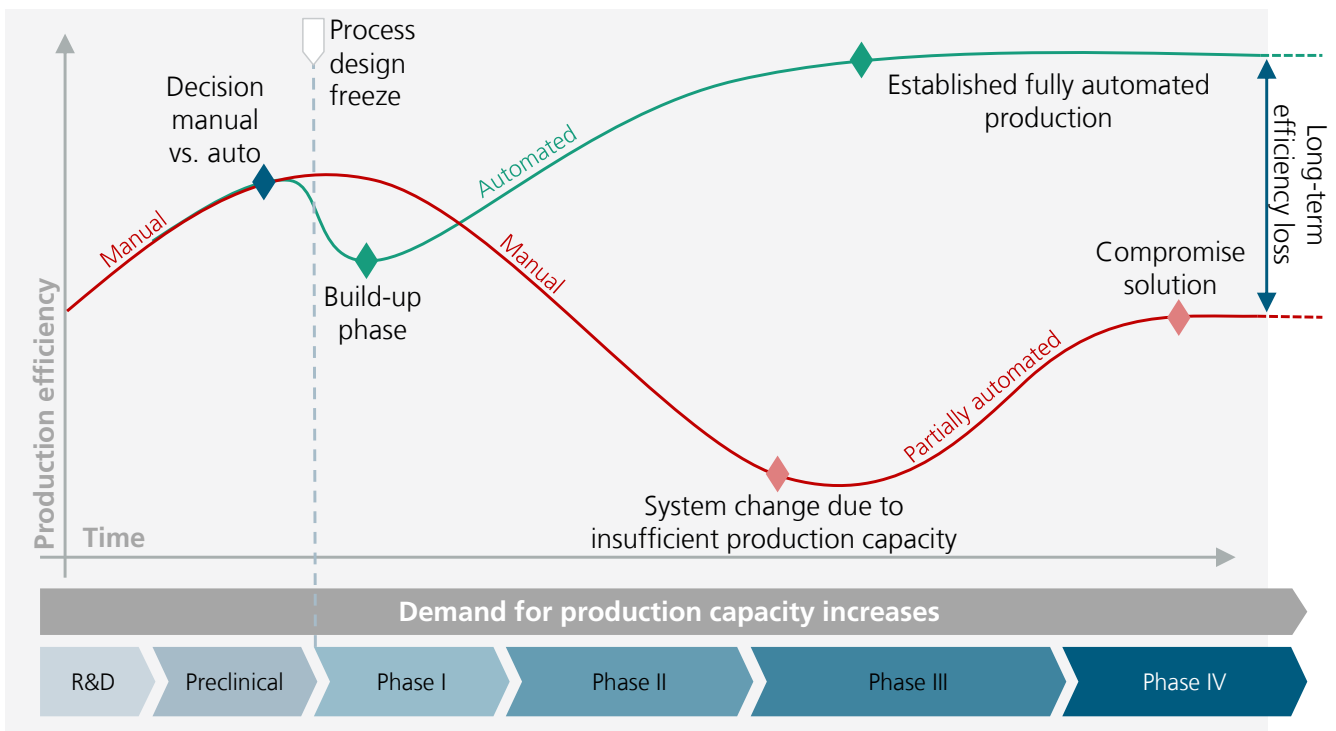


Figure 10: “Valley of Tears” in ATMP production

Use cases: Automated cell production

The Fraunhofer IPT has been researching production technologies for biological products since 2010. Numerous fully automated platforms have already been developed, both for partners from industry and as part of publicly funded research projects. Three of these research facilities are the “StemCellFactory”, “Autostem”, “AIDPATH” and “JointPromise”.

StemCellFactory

Automation is becoming increasingly important in modern biotechnology, especially in the production of stem cells for regenerative medicine. One example of this is the StemCellFactory, an automated platform that covers the entire hiPSC production process. In order to use hiPSCs for commercial purposes, large quantities must be produced. The scalable production of these cells is difficult to achieve with conventional production methods due to high error rates and contamination.

In the StemCellFactory, hiPSCs can be produced in up to 500 cell culture plates within three weeks without human intervention. The developing cell colonies are automatically recognized, harvested and further cultivated accordingly. The quality of the cells can be continuously monitored using high-speed microscopy and image-based analysis. A decisive process step in the production of iPSCs is the editing of the genome of the original cell. For this purpose, automated genome editing was established on the StemCellfactory for the first time, enabling the system to carry out the entire production process fully automatically. The automation of the process enables the production of hiPSCs in the required large quantities so that they can then be used for disease models or drug tests, for example. [22–24]



Abbildung 11: StemCellFactory: automated platform for iPSC manufacturing. Located in Bonn, Germany

AUTOSTEM

Another example of automation in regenerative medicine is the "AUTOSTEM" project. The system enables a fully automated bioreactor-based production of mesenchymal stem cells (MSCs). The cells are continuously multiplied in bioreactors, supplied with nutrient medium and counted regularly to determine their growth rate. As soon as the desired number of cells is reached, the cells are automatically removed from the bioreactor, separated from the culture medium and stored in special cooling vessels at -80°C .

The automation of this process also offers decisive advantages. It also minimizes the risk of errors and contamination, increases efficiency and enables highly scaled production of MSCs on a liter scale. It also enables close monitoring of process parameters and cell quality in real time, which is crucial for quality assurance and clinical application.

The automation of stem cell production is therefore an important step towards cost-efficient and standardized processes for the production of therapeutic cell cultures. In this way, innovative stem cell-based therapeutic approaches can be further advanced and made accessible for a wide range of applications. [25]

AIDPATH

The AIDPATH project is working on developing an automated and intelligent system for the production of CAR-T cells. This technology makes it possible to produce a targeted and patient-specific cell therapy directly at the point of treatment.

The use of artificial intelligence (AI) and the integration of individual patient data into the treatment process is crucial for optimizing CAR-T cell production. This enables the development of highly effective and customized CAR-T cell products that are specifically tailored to the needs of each individual patient.

Ultimately, this should enable improved access for patients to CAR-T cell therapy. The automation and decentralization of production will help to shorten production times and make the therapy available more quickly and efficiently. [26]

Use case: Automated tissue production

Due to demographic change and changing lifestyles, there is an increasing need for therapeutic agents for established common diseases to relieve the burden on the health system. Osteoarthritis and cardiovascular diseases caused by obesity, lack of exercise or poor nutrition are just two of the trend diseases identified in epidemiological studies. Novel therapy methods in regenerative medicine involve the use of tissue replacement structures to restore body functions and offer an alternative to conventional treatment methods. By combining materials science, biotechnology and engineering, innovative tissue replacement structures with complex mechanisms of action are produced in what is known as “tissue engineering”. In addition to replacement structures for restoring mechanical functions, which are used for example in bony areas of mouth, jaw and facial reconstruction or in the dental field, implants based on living material open up completely new possibilities for tissue regeneration. Cell-based tissue implants consist of a support or matrix structure on or in which highly potent cells are integrated. The cell type is adapted to the damaged tissue to be replaced so that the body does not trigger a defense reaction to a foreign material. By introducing body-like cells into a tissue-specific structure, damaged tissue is not only replaced, but ultimately regenerated by means of cell-cell interactions.

Challenges

The challenges of tissue engineering lie on the one hand in the selection of suitable carrier materials for living cells. In addition to the mechanical properties of the material, which influence cell proliferation and adhesion, vein-like structures are essential for large-area implants in order to ensure a continuous supply of nutrients to the living material. Novel types of material, such as hydrogels made from the body’s own collagen, not only provide an ideal basis for cultivating cells, but also prevent the defense reactions that would occur with synthetic implants. So-called bioprinters are also an advanced form of conventional 3D printers that can produce complex multi-layered implants from different types of material and cells to create tissue-like structures.

On the other hand, a large number of cells are required in tissue implants in order to minimize the amount of carrier material and thus increase the regeneration potential - several million cells are often required for structure sizes in the centimeter range. The scalability of the manufacturing process for cell-loaded tissue replacement structures is therefore essential to meet the increasing global demand.

Advantages of process automation

In addition to high throughputs, process automation offers advantages in terms of quality consistency and efficiency, but also reduces high personnel costs in cell production processes that are currently mainly carried out manually. Current research trends in cell culture are the use of three-dimensional cell aggregates, so-called spheroids (spherical bodies), which, in addition to a high cell density, also improve the interaction of the cells with each other and with the surrounding material. Overall, this can lead to an increased survival rate of the cells and an optimized regeneration process of the tissue.

JointPromise: automated production of advanced 3D joint implants for osteoarthritis treatment

The “JointPromise” research project approved under the EU Horizon 2020 funding program involves the design and implementation of an automated production platform for three-dimensional joint implants for the treatment of osteoarthritis. Recent studies have identified musculoskeletal disorders as one of the ten most common diseases in the middle age group. Among musculoskeletal diseases, osteoarthritis is one of the most common chronic joint diseases leading to progressive degeneration of cartilage with over 300 million cases reported worldwide. With the increasingly ageing world population, it can be assumed that the number of osteoarthritis cases will continue to rise in the future - as is also evident in study trends. [27] Tissue engineering can offer a promising alternative to conventional long-term medication, physiotherapy or joint replacement surgery. The automated production of cell-based 3D structures for the regeneration of cartilage is realized

in "JointPromise" through highly scaled cell production combined with multi-layer bioprinting. The production facility is subject to the highest hygiene standards, for example in terms of cleanability, the materials selected and air filtration.

The production system includes a six-axis robot for transporting the cell culture systems to the various system components. As the majority of the cell multiplication process consists of transporting liquids, pipetting robots are integrated into the system for different quantities of liquid. An incubator is implemented for cell proliferation in a temperature-controlled environment similar to human body temperature. In addition to storage systems for process fluids and consumables, an automated microscope for 100% quality control rounds off the cell production process chain. The cartilage cell aggregates produced are finally processed in the bioprinter to form three-dimensional replacement structures. The layer-by-layer

printing of carrier material, sliding layers and cell aggregates makes it possible to reproduce the complex tissue structure of the human body. Contrary to the expectation that cartilage only fulfills a buffer function of mechanical joint loads, a variety of functional cell and material types are represented, which can be specifically reproduced in the bioprinter. The development and construction of the "JointPromise" system at the Fraunhofer IPT provides the basis for automated high-throughput cell production in order to meet the increasing demand for alternative therapeutic approaches in regenerative medicine.

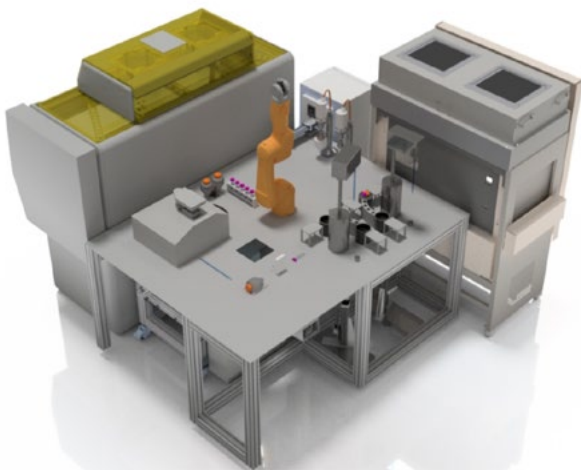
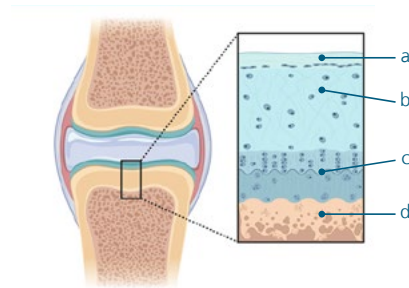


Figure 12: JointPromise: Image A shows a render of the production facility with a central robot for all material handling and all other devices arranged around it.



- a. Articular surface
- b. Articular cartilage
- c. Tidemark
- d. Presumptive bone zone hypertrophic chondrocytes

Figure 13: The cartilage layer that is reproduced with the implants produced on the system.

Intelligent and integrated analytics

Inline metrology

High-speed microscopy

Quality control and analysis play an important role in the cultivation of cell populations. In particular, the examination of larger samples at high magnification takes a lot of time. As cell culture plates are often examined by trained specialists, this makes the process labor- and cost-intensive and prone to subjective errors in the final inspection. By using a continuous scanning process, large samples can be digitized quickly and easily using high-speed microscopy (HSM). The analysis of the image data can also be fully automated using downstream image processing procedures. This results in personnel and time-saving processes that increase the throughput of larger production facilities and ensure reproducible quality control of the cells.

HSM technology

Due to the microscope's small field of view, large samples must be examined piece by piece. Conventional microscopes use a "stop-and-go" method in which the individual image sections are approached one after the other, the focus is adjusted and then the image is captured. Due to the constant acceleration and deceleration, this method is very time-consuming and particularly unsuitable for samples filled with liquid. The Fraunhofer IPT has therefore developed a high-speed microscope in which the sample is moved continuously under the lens and images are recorded while moving. To avoid motion blur during image acquisition, a pulsed light source with external triggering and high illuminance is used. The short illumination time ensures that the relative movement between the lens and the sample does not exceed the resolution limit of the camera and sharp images are produced. In addition, the focus position for each image section is dynamically tracked by a z-piezo actuator to compensate for unevenness and take account of the shallow depth of field. The data for the focus tracking comes from an upstream focus scan, in which the sample is scanned by a confocal chromatic sensor and a height profile is created from the data [28].

The microscope body forms the basis and has been expanded to include a movable sample stage, a flash light source and a high-speed camera. The measurement processes are controlled and the image data evaluated via a connected computer. A controller synchronizes the image acquisition with the illumination and focus correction. Thanks to the simple and comparatively inexpensive design, a large number of commercially available microscopes can be extended for high-speed image acquisition and thus various set-ups with reflected light, transmitted light, phase contrast and polarization microscopy can be implemented.

Image processing

The image capture process is followed by several post-processing steps. These include correcting shading and increasing contrast, as well as stitching, in which the individual images are combined to form an overall image. Integrated image evaluation with pattern recognition or AI algorithms for individual tasks such as cell segmentation and confluence calculation is also possible. Thanks to GPU support, even computationally intensive processes run in parallel to the scanning process and enable real-time data handling. The results of the image processing are therefore available to the user immediately after the scan.

Deep learning methods are increasingly being used for more extensive analysis. As a rule, such neural networks must be adapted to the given data set in order to achieve optimum performance. As this requires domain knowledge, the creation of deep learning approaches is often difficult for biological experts. The Fraunhofer IPT has therefore developed software that suggests a suitable selection of algorithms for new data sets and applies them to the data set. For this purpose, a decision logic was trained on a large number of deep learning pipelines together with domain-specific use cases. This makes it possible for users to create powerful algorithms for individual use cases without any knowledge of artificial intelligence [29].

Integration into automated processes

The microscope can be used in fully automated systems for analyzing cultured cells. This enables high-throughput processes with consistently good quality control and documentable quality parameters.

The integration of laser-induced forward transfer (LIFT) into the existing high-speed microscopy system was successfully tested so that the separation and removal of individual cells on a culture plate can also be fully automated. By integrating a laser into the beam path of the high-speed microscope, analysis and cell isolation can be combined in a single device without the need for additional sample preparation. The method uses pulsed laser radiation to transport cells across an air gap between two surfaces by directing it at the interface between the microtiter plate and the cell medium [30].

Adaptive phase contrast microscopy

Phase-contrast and fluorescence microscopy are among the most important methods for analyzing biological samples and observing living cells. In contrast to fluorescence microscopy, however, it does not require fluorescence markers and is therefore gentler for the automated cultivation of high-value cells. However, the observation area is limited to the center of the cell vessels due to the so-called "meniscus effect". This makes it difficult to determine the quality parameters outside this area. The Fraunhofer IPT is therefore researching methods

in adaptive phase contrast microscopy in order to significantly increase the microscopically visible area. In order to be able to use the method in automated systems, an ongoing research project is aiming to make the process highly efficient [31].

Although the method is already faster than comparable "stop-and-go" methods, the Fraunhofer IPT is constantly working on improving the recording processes. Thanks to the simple expandability of microscopy systems, customer-specific solutions can be developed in projects for various industries. A wide range of individual requirements can be addressed and the integration of high-speed microscopes into existing automated systems can be implemented.

Optical Coherence Tomography

Optical Coherence Tomography (OCT) is an imaging technique based on short-coherent interferometry that produces high-resolution cross-sectional images of (semi-)transparent materials. The origins of the procedure lie in ophthalmology, particularly in the non-invasive inspection of the fundus of the eye. In addition, imaging has evolved rapidly with the development of a variety of new functions and modalities. Biomedical research and diagnostics continue to be the main areas of application, but in addition to ophthalmology, applications within dermatology and cardiology are also playing an increasingly important role.

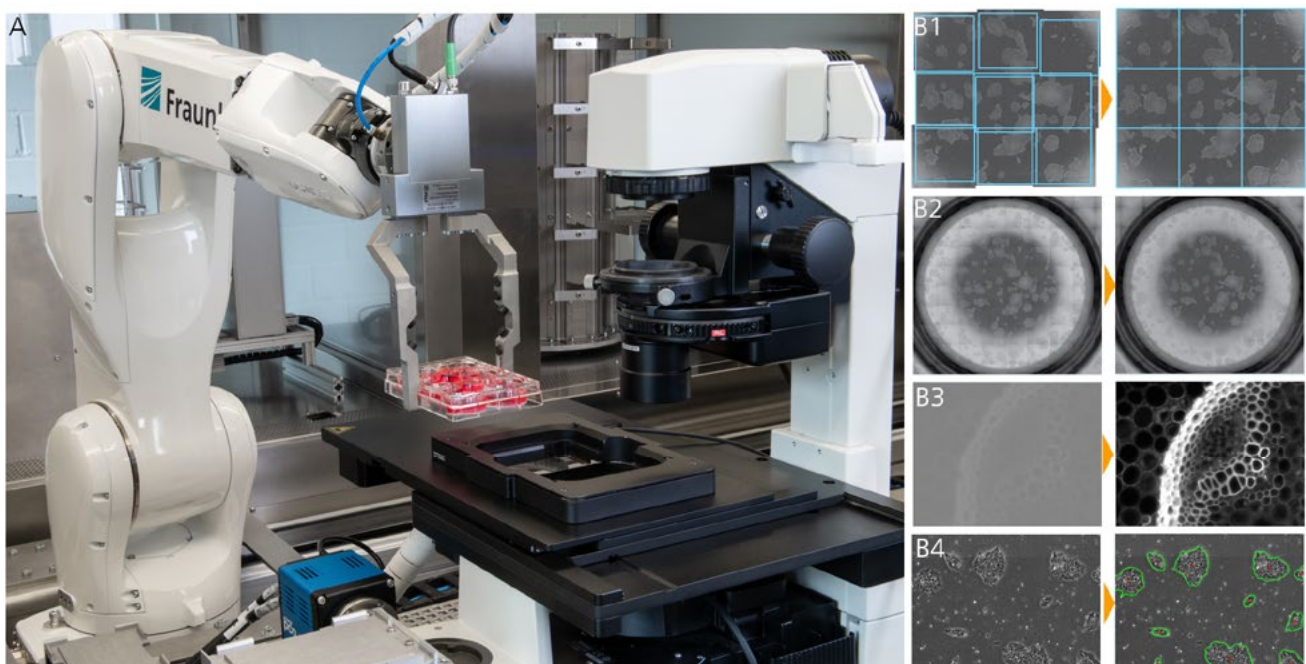


Figure 14: The high-speed microscope on an automated platform with robotic arm (A) and a selection of image processing steps. B1: image stitching, B2: shading correction, B3: histogram normalization and B4: cell segmentation.

The properties of OCT, in particular the ability to generate high-resolution cross-sectional images without contact, also make the technology attractive for a wide range of research topics and applications outside the biomedical field. These include surface and material testing as well as defect detection in polymers or other scattering samples.

OCT works in a similar way to ultrasound imaging, but instead of detecting sound waves, it detects the change in the path length of the short-coherent light sources used or the size of the backscattered light. The basic structure of an OCT system consists of a Michelson interferometer with a short-coherent light source, a detector, a sample path and a reference path. The light is split into the two paths by a beam splitter and reflected in each case. In the sample path, there is a pair of scanning mirrors next to the focus optics, which allows the light spot to be scanned in a transverse direction perpendicular to the sample. Thus, in addition to point measurements (depth profile of the sample), cross-sectional images or volume scans can also be generated. The superimposed light from the sample and reference path is usually detected in a spectrometer. Axial scanning of the sample is not necessary here, as the depth information of the frequency modulation can be taken from the interference spectrum in the detector.

Depending on the light source used and the focus optics, resolutions of approx. 3 to 10 μm can be achieved. The imaging depth is limited by the optical attenuation due to

tissue scattering and absorption. In most tissues, imaging can be achieved to a depth of 2 to 3 mm. OCT therefore closes the gap between microscopy, which has a high resolution but does not allow access to internal structures, and ultrasound imaging, which can look deep into (human) tissue but has a significantly lower resolution than OCT.

Use of OCT in the laboratory environment

The main reasons for using OCT in biological, chemical or medical laboratories are the high resolution and the high measuring depth, especially in comparison to microscopy. Another important advantage of OCT is its non-invasiveness, which enables dynamic processes in samples to be analyzed, among other things. Due to the resolution in the micrometer range with non-destructive operation, OCT can be used as an "optical biopsy" to examine tissue both qualitatively and quantitatively [32]. High-resolution OCT systems with a spatial resolution of approx. 1 μm come close to pathological histology. Examples of OCT use include in vivo examinations to differentiate between benign and malignant epithelial tissue for the diagnosis of various types of cancer [33] as well as in vitro studies to analyze artificial tissue or monitor wound healing processes. OCT is of interest for applications in developmental biology as it allows repeated imaging of the developing morphology of a sample without sacrificing or altering it [32]. This makes it possible, for example, to observe the development of tissue over long periods of time (e.g. development over several days or weeks) or even to detect changes in the tissue over a short period of time (e.g. milliseconds to several seconds) within an OCT data set. In the laboratory, changes in cell cultures can thus be tracked over time without the need for staining or fixation. By analyzing such OCT image stacks within "dynamic OCT", the viability of cells in tissues can be analyzed and their intracellular activities observed, for example. The functional enhancements also include the visualization of (internal) tensions and the measurement of blood flow. In addition to these functional extensions for the quality monitoring of in vitro tissue or cell culture samples, the non-contact, optical measurement method also enables direct, contamination-free integration into the laboratory environment, e.g. in bioreactors [34]. High-contrast imaging can also be performed in closed, transparent vessels, which significantly simplifies handling in the laboratory.

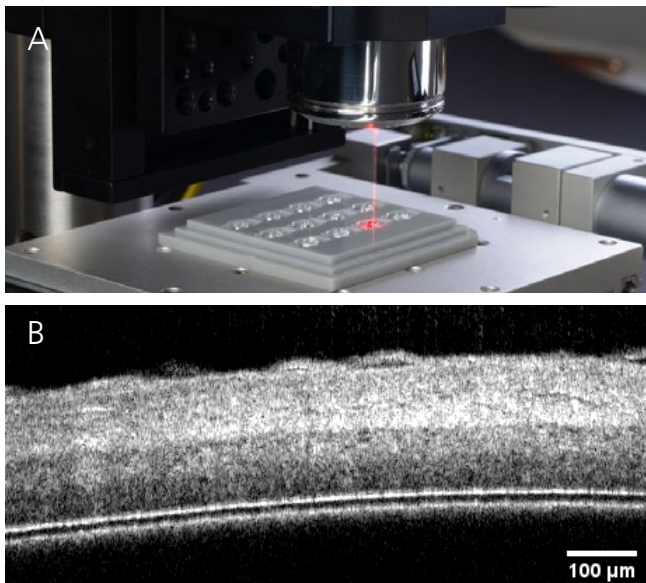


Figure 15 – A: Scan head of an OCT system. The objective focuses on the sample from which the backscattered light is measured at the detector. B: OCT cross-section of an invitro tissue. The thickness of the tissue as well as internal structures and interfaces can be detected by OCT.

Trends and potentials of OCT in the laboratory

In recent years, OCT has been continuously developed and imaging has been expanded with additional contrasts. In addition to hardware-side optimization, for example towards faster image generation, “functional OCT” in particular is constantly evolving and is increasingly finding its way into biological and biochemical laboratories. This includes, for example, the extraction of mechanical properties and dynamic OCT for monitoring tissue and cell dynamics. This is particularly valuable for investigating cell morphology, tissue development and the effects of various treatments on biological samples.

In the field of pharmacy or cancer research, OCT can be used in the future to investigate the penetration and distribution of drugs in tissue and organs. This information is crucial for evaluating the effectiveness of drugs. Also in the field of tissue engineering and regenerative medicine, OCT is increasingly proving to be a powerful tool for characterizing biomaterials, polymer scaffolds and implants.

There are also new possibilities for data and image processing through AI-based approaches, which simplify and optimize tissue segmentation and classification, for example, detect anomalies better and faster and can make predictions about disease progression or tissue changes. Multimodal imaging, such as the integration of OCT into microscopes, offers a more holistic view of biological structures and facilitates the handling of cell cultures and other samples in the laboratory. Overall, more and more applications are benefiting from OCT’s advantages of non-invasiveness and high resolution at high measurement depth, allowing OCT to complement or even replace more and more costly, destructive quality methods in biological laboratories.

Atline support systems

Micro labs on chip and disk

Within microfluidic systems, liquids and gases can be directed and moved through microscopic channels and membranes in a targeted manner. In the life sciences, this describes the miniaturization of analytical methods from areas such as laboratory analysis, quality control in production facilities and laboratories, medical diagnostics including point-of-care testing (POCT), and environmental analysis. Miniaturization enables smaller sample volumes, lower material costs, faster analysis, simpler, more robust and decentralized implementation, and in many cases a reduction in costs per test. Microfluidic systems can be tailored to specific methods and therefore offer a high degree of flexibility for a wide range of applications.

Production of microfluidic systems

Microfluidic systems are produced using chip-based systems with liquid transport that is passively driven by capillary forces within porous membranes or microchannels. Systems with controllable pump systems or centrifugal force-driven disk platforms are suitable for active fluid transport. One option for producing microfluidic systems on an industrial scale is nano-imprint lithography on continuous roll-to-roll machines, which enables cost-effective production. Centrifugal lab-on-a-disc systems can also be molded with optical polymers using injection molding processes. After polymer molding, automatic pick & place systems are suitable for loading functional units under aseptic conditions and final lamination to seal the products.

Depending on the sample material to be analyzed, application-specific functional units such as filter systems, biological or optical markers or substance separation techniques can be implemented. Optical or electrochemical methods (and others) can be used for quantitative or qualitative analysis.

The measurement sensors can be located directly on the microfluidic test chip, for example via microelectrode arrays that can be configured electrically and with little instrumental effort. By coupling to colorimetric or fluorescence-based dyes, it is possible to carry out optical analyses using external optical analysis systems.

Another analysis option is Raman spectroscopy. A Raman spectrum is recorded with the aid of lasers. Based on the characteristic peaks in the spectrum, conclusions can be drawn about the molecules contained. The so-called SERS substrates (surface-enhanced Raman scattering) are particularly suitable for Raman spectroscopy, as they allow the Raman signal to be amplified by a factor of 10^6 to 10^8 . SERS substrates consist of a metal-nanoparticle array produced by nanoimprint lithography. The sample molecules bind to the metallic nanoparticles and are thus detected more strongly.

Areas of application for microfluidic systems

Microfluidic systems offer numerous advantages in diagnostics. At the Fraunhofer IPT, microfluidic systems are being developed and researched for numerous areas of application. Examples include the development of systems for the rapid diagnosis of infectious diseases, the determination of trace elements in drinking water and the analysis of foodstuffs. Another important area of application is quality control in production plants, where microfluidic systems are used to quickly and precisely determine production errors. In addition, microfluidic systems are also used at the Fraunhofer IPT for the development of point-of-care tests (POCT) and environmental analysis.

“Lab-on-a-chip” as an example for microfluidic analytics

The “lab-on-a-chip” approach is a completely miniaturized analysis device that is integrated on a chip. It enables samples to be analyzed quickly and is therefore ideal for use in medical diagnostics. Another example is the “lab-on-a-disc” system, in which the analysis is carried out on a rotating disk. This is also a completely miniaturized analysis platform that enables samples to be analysed quickly and precisely.

With a view to sustainable and circular value chains, microfluidic or micromechanical systems are increasingly made of bio-based and/or biodegradable plastics instead of the plastics commonly used in laboratories and industry. Paper-based microfluidic systems also offer a wide range of applications.

In summary, microfluidic systems offer numerous advantages in diagnostics and analysis. They offer a high degree of flexibility and enable samples to be analyzed quickly and precisely. At the Fraunhofer IPT, microfluidic systems are developed and researched for numerous areas of application in order to enable sustainable and efficient diagnostics and analysis.



Figure 16: Production of microfluidic structured films using a roll-to-roll process.

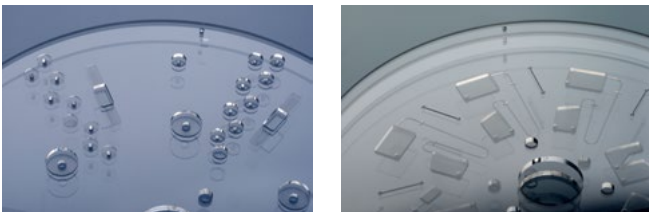


Abbildung 17: Lab-on-disk for in-vitro diagnostics.

Use case: SecuriGel pathogen analyzer

Molecular diagnostics has undergone a revolutionary development in recent years and has now become indispensable in a variety of medical and healthcare settings. From hospitals and care centers to public institutions and even individual home use, the use of nucleic acid amplification systems has become a crucial part of modern diagnostics. However, this technology does not only play a central role in the healthcare sector; impressive fields of application are also opening up in environmental analysis for the detection of viruses and organisms and as quality control in industry, for example in food processing. In recent years, especially during the pandemic, it has become clear how important reliable and rapid diagnoses of infectious diseases can be for societies.

The various solutions available on the market today are limited by technical constraints: the molecular reactions can be sensitive to impurities, time-intensive due to the need for cyclic amplification, require expensive instrumentation and, last but not least, make application more difficult due to higher-quality raw materials or special storage conditions. In response to this, Fraunhofer CMI, IGB and IPT have developed a new rapid test using interdisciplinary expertise from the fields of molecular biology, materials science, bioprinting, production and optics.

SecuriGel pathogen analyzer (left). The SecuriGel pathogen analyzer from the Fraunhofer IPT (right).

In the “Pathogen Sensors” research project, the Fraunhofer CMI in Boston (USA) is optimizing the design in terms of sensitivity and selectivity of the bioassay for the currently widespread respiratory viruses SARS CoV2, influenza A, influenza B and rhinovirus. In addition to the bioprinting process, the Fraunhofer IGB is designing the chemical composition of the hydrogel to meet the requirements of the bioassay and the conditions of a self-test. The Fraunhofer IPT is developing a smartphone-operated analysis instrument and the microfluidic test chip for this purpose.

The Fraunhofer IPT has been researching continuous molding processes and printing processes for plastic embossing for many years and technically implementing them for various areas of application. In the project, the diagnostic test chip was designed from the outset with a view to continuous and scalable production in a roll-to-roll process and can therefore be manufactured cost-effectively. In addition, a portable and decentralized analysis instrument was developed that performs the rapid test on a patient-specific basis and can be operated via smartphone.

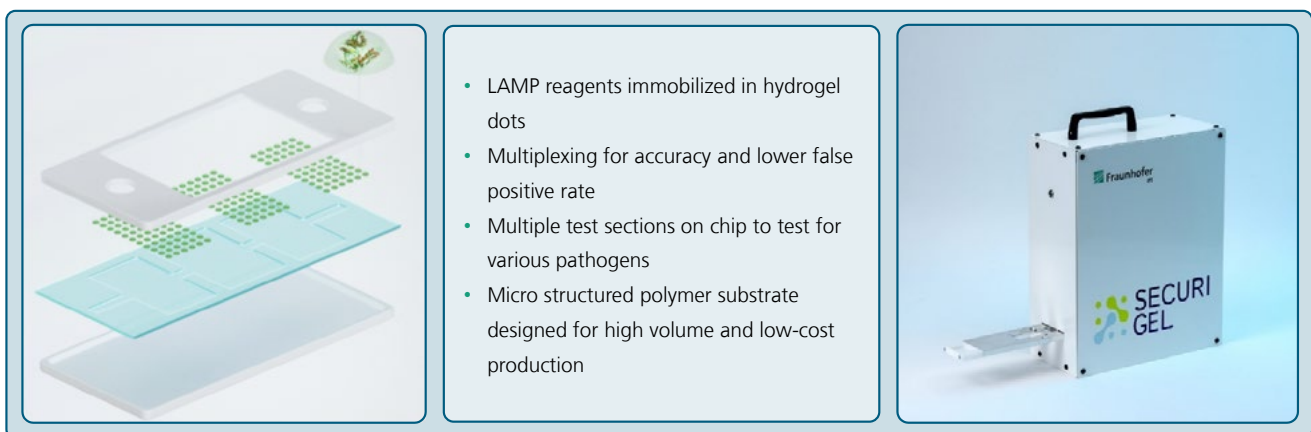


Figure 18: The composition of the microfluidic test chip of the

Sustainability

Conflict between sustainability and regulatory compliance

Sustainable development means meeting the needs of the present without jeopardizing the opportunities of future generations. The focus is on three strategies: sufficiency (less production and consumption), efficiency (better use of resources) and consistency (environmentally friendly cycles). Sustainable management aims to ensure an intact ecological, social and economic system for future generations. The EU taxonomy classifies economic activities as sustainable if they meet certain environmental targets and comply with social standards. Legislative initiatives such as the European Green Deal and Regulation (EU) 2020/852 promote this transformation.

The biopharmaceutical industry faces challenges in terms of sustainable production, as its energy-intensive manufacturing processes and high resource consumption are often not very environmentally friendly. However, there are increasing efforts to make progress through technological innovations and more sustainable supply chains.

Various approaches for sustainable biotechnological production processes and medical technology

1. Use of environmentally friendly materials: One approach is to use sustainable materials in the manufacture of biotechnology products and medical devices. This can include the use of recyclable or biodegradable materials to reduce waste and minimize environmental impact.
2. Energy efficiency: By optimizing production processes and using energy-efficient technologies, energy consumption in biotech production processes and medical devices can be reduced. This can include the use of renewable energy and lead to a reduction in CO₂ emissions.
3. Waste minimization and recycling: The implementation of waste minimization and recycling strategies is an important approach for sustainable production. This can include the reuse of materials, the reduction of packaging materials and the implementation of take-back programs for used equipment.
4. Life cycle analysis: A life cycle analysis is an approach in which the environmental impact of a product is assessed over its entire life cycle. This includes the phases from raw material extraction through production to disposal.

Sustainability can be improved by identifying and optimizing aspects that have a negative impact on the environment.

5. Cooperation and knowledge transfer: Sustainable development often requires cooperation between different actors, such as companies, governments, research institutions and NGOs. The exchange of knowledge, experience and best practices can help to promote sustainable approaches in biotechnological production and medical technology.
6. Promoting a circular economy: Promoting a circular economy, where products and materials are reused, repaired or recycled at the end of their life, is another important approach to sustainability. It is important to note that sustainable approaches are always contextual and depend on the specific requirements and circumstances of a product or technology. Companies and organizations should consider a holistic view of sustainability and combine different approaches to find an optimal solution.

Harmonizing compliance and sustainability

Irrespective of regulatory requirements, compliance expresses conformity with rules, both in relation to laws, regulations and official requirements as well as to voluntarily defined internal strategies and framework conditions. Corporate governance is defined as the organizational and substantive totality of the strategic orientation of responsible corporate management. In this context, both compliance and the entire area of sustainability should be viewed as reference systems under the umbrella of effective corporate governance.

The new discipline of sustainability also poses challenges for the compliance function. There are new criteria for sustainability reporting in which an activity is considered sustainable if it makes a significant contribution to achieving one or more of the six environmental goals or does not jeopardize or negatively impact these goals. These environmental goals include climate change mitigation, climate change adaptation, sustainable use and protection of water and marine resources, transition to a circular economy, pollution prevention and reduction, and protection and restoration of biodiversity and ecosystems.

Sustainability and compliance are also closely linked in biomedicine. Sustainability in biomedicine means that medical practices, research and development and the use of resources are designed to meet the needs of the present without limiting the possibilities of future generations.

The conflict between sustainability and regulatory compliance in the field of biotechnological processes and medical technology is complex. Sustainability refers to the preservation of natural resources and the development of environmentally friendly technologies. Regulatory compliance refers to compliance with laws and standards that apply to the development and use of biotechnological processes and medical devices. These regulations serve to ensure the safety and efficacy of these technologies and to protect the health of patients. The conflict arises when sustainable approaches may not comply with existing regulations. Cost and safety considerations also play a role. Sustainable technologies may require higher initial investment or be more expensive to implement. Nevertheless, there are ways to reconcile sustainability and regulatory compliance, e.g. by developing sustainable materials and processes that comply with regulations or by collaborating and developing industry-specific sustainability standards. Overall, the conflict between sustainability and regulatory compliance in the field of biotechnological processes and medical technology is a complex challenge. It is important to carefully weigh up the interests and find innovative solutions in holistic approaches.

Several regulatory requirements play an important role in the field of biotechnological processes and medical technology. The exact requirements may vary from country to country and region to region, but some key regulations are internationally recognized.

The most important regulatory requirements:

- 1.** Medical Device Regulation (MDR): The MDR regulates the requirements for the safety, performance and quality of medical devices in the EU as well as their approval and monitoring.
- 2.** In-vitro Diagnostic Regulation (IVDR): Similar to the MDR, the IVDR sets out the requirements for in-vitro diagnostic devices in the EU, including approval and monitoring.
- 3.** Good Manufacturing Practice (GMP): GMP are international standards that regulate the manufacture, storage, packaging and distribution of medicinal products and medical devices.
- 4.** ISO 13485: This standard defines quality management systems for medical technology and serves as proof of conformity with regulatory requirements.
- 5.** Environmental and sustainability standards: Many companies voluntarily implement standards such as ISO 14001 for environmentally friendly practices.

Regulatory requirements vary depending on the product type, area of application and region, which is why companies must adapt their products to the applicable requirements.

Compliance, on the other hand, refers to adherence to legal and ethical standards in bio-medicine, including laws, regulations and guidelines. This includes the protection of patient privacy and data, adherence to GCP (Good Clinical Practice) in clinical trials and the fulfillment of quality and safety standards. Integrating sustainability into compliance in biomedicine means that ecological and social aspects are taken into account in addition to compliance with legal and ethical standards. This can include, for example, the use of environmentally friendly materials and processes, the minimization of waste and emissions as well as the promotion of social justice and access to medical care.

Challenges

The major challenge is likely to lie in the creation of criteria that are as standardized as possible for regulatory compliance with regard to sustainability. There are various challenges in implementing sustainability in the biomedical laboratory. Some of these are

1. **Costs:** implementing sustainable practices in the laboratory may initially involve additional costs. This may include the use of more environmentally friendly materials or the installation of energy-saving equipment. Costs need to be carefully weighed and potential savings over time taken into account.
2. **Infrastructure:** Implementing sustainability may require changes to the existing infrastructure of the laboratory. This may include the use of recycling or waste separation systems, the installation of energy-saving light bulbs or the adaptation of equipment to minimize energy consumption. The infrastructure changes may require additional investment and adaptation.
3. **Complexity of the experiments:** In some cases, sustainable practices may conflict with the specific requirements of certain experiments. For example, the use of disposables to avoid contamination and the use of larger quantities of solvents or chemicals to achieve precise results may clash. Here it is important to look for alternative methods or materials to find the balance between sustainability and experimental requirements.
4. **Training and awareness:** Implementing sustainable practices requires extensive training of the laboratory team. Employees must be aware of the importance of sustainability and acquire the necessary skills to act in an environmentally conscious manner. This requires continuous training and awareness of sustainable practices in the laboratory.
5. **Availability of sustainable materials:** It can be a challenge to find sustainable materials and reagents for laboratory operations. It may require additional research and collaboration with suppliers to identify and source environmentally friendly alternatives to conventional products.

Despite these challenges, however, there are many opportunities to implement sustainability in the biomedical laboratory. Through deliberate planning, collaboration and continuous improvement, laboratories can help minimize their environmental impact and contribute to more sustainable biomedical research.

Added value for research and production laboratories

In summary, sustainability in the biomedical laboratory is a holistic approach that goes beyond mere compliance and offers long-term benefits for laboratories and society and can only be achieved collectively. Ultimately, sustainability and compliance in biomedicine strive to ensure the responsible and ethical use of resources, patients and the environment in order to achieve a sustainable and long-term positive impact on people's health and well-being.

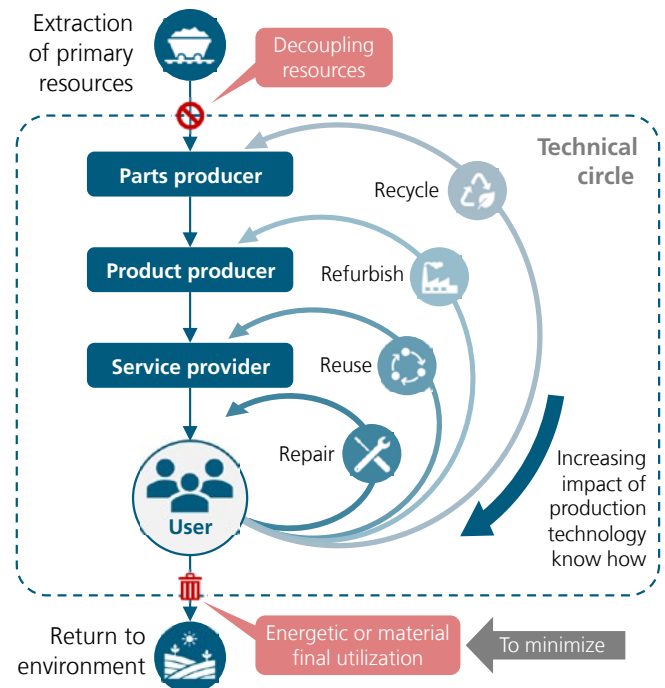


Figure 19: Sustainable production process to promote a circular economy by decoupling the process from primary resources

References

- [1] F. Biermann, J. Mathews, B. Nießing, N. König, and R. H. Schmitt, "Automating Laboratory Processes by Connecting Biotech and Robotic Devices—An Overview of the Current Challenges, Existing Solutions and Ongoing Developments," *Processes*, vol. 9, no. 6, 2021, doi: 10.3390/pr9060966.
- [2] Y. Han, E. Makarova, M. Ringel, and V. Telpis, "Digitization, automation, and online testing: The future of pharma quality control: Emerging technologies can make quality control (QC) faster and more efficient. What do pharma companies need to do to become QC leaders?," 2019. Accessed: Jan. 22 2025. [Online]. Available: <https://www.mckinsey.de/~ /media/McKinsey/Industries/Pharmaceuticals%20and%20Medical%20Products/Our%20Insights/Digitization%20automation%20and%20online%20testing%20The%20future%20of%20pharma%20quality%20control/Digitization-automation-and-online-testing-The-future-of-pharma-quality-control.pdf>
- [3] *System und Software-Engineering – Begriffe*, ISO/IEC/IEEE 24765:2017, ISO Internationale Organisation für Normung; IEC Internationale Elektrotechnische Kommission; IEEE The Institute of Electrical and Electronics Engineers, Inc., Sep. 2017.
- [4] A. Sinsel, *Das Internet der Dinge in der Produktion: Smart Manufacturing für Anwender und Lösungsanbieter*. Berlin, Heidelberg: Springer Vieweg, 2020.
- [5] MQTT, MQTT: The Standard for IoT Messaging. [Online]. Available: <https://mqtt.org/> (accessed: Jan. 22 2025).
- [6] OPC Foundation, OPC 10000-1: UA Part 1: Overview and Concepts. [Online]. Available: <https://reference.opcfoundation.org/Core/Part1/v104/docs/> (accessed: Jan. 22 2025).
- [7] Association Consortium Standardization in Lab Automation (SiLA), SiLA 2 Part (A) – Overview, Concepts and Core Specification: Working Draft Version. [Online]. Available: <https://docs.google.com/document/d/1nGG Ewbx45ZpKeKYH18VnNysREbr1EXH6FqjCo03yASM/edit#heading=h.6hlm463x8ygx> (accessed: Jan. 22 2025).
- [8] OPC Foundation, OPC 30500-1: Laboratory and Analytical Devices. [Online]. Available: <https://reference.opcfoundation.org/LADS/v100/docs/> (accessed: Jan. 22 2025).
- [9] A. Hideg and F. Dorf Müller, LADS: Laboratory and Analytical Device Standard: Bridging the Gap, Connecting the Lab! (accessed: Mar. 12 2025).
- [10] J. Krauß, J. Dorißen, H. Mende, M. Frye, and R. H. Schmitt, "Machine Learning and Artificial Intelligence in Production: Application Areas and Publicly Available Data Sets," in *Production at the leading edge of technology: Proceedings of the 9th Congress of the German Academic Association for Production Technology (WGP), September 30th - October 2nd, Hamburg 2019*, J. P. Wulfsberg, W. Hintze, and B.-A. Behrens, Eds., Berlin, Heidelberg: Springer Vieweg, 2019, pp. 493–501.
- [11] R. Jonak, Labor-Informations- und Management-Systeme: Overview. Positionierung, LIMS-Einsatzbereiche und Trends. [Online]. Available: <https://analyticalscience.wiley.com/content/article-do/labor-informations--und-management-systeme> (accessed: Jan. 22 2025).
- [12] Fraunhofer-Institut für Produktionstechnologie IPT, Software für die Laborautomatisierung: cope. life – Zentrale Steuerung für die gesamte Zell- und Genproduktion. [Online]. Available: <https://www.ipt.fraunhofer.de/de/angebot/sondermaschinen/laborautomatisierung/software.html> (accessed: Jan. 22 2025).
- [13] *Software engineering — Software product Quality Requirements and Evaluation (SQuaRE) — Data quality model*, ISO/IEC 25012:2008, ISO Internationale Organisation für Normung; IEC Internationale Elektrotechnische Kommission, Dec. 2008.
- [14] J. Riley, *Understanding metadata: What is metadata, and what is it for?* A Primer Publication of the National Information Standards Organization. Baltimore: National Information Standards Organization, 2017. Accessed: Jan. 22 2025. [Online]. Available: <https://groups.niso.org/higherlogic/ws/public/download/17446/Understanding%20Metadata.pdf>
- [15] M. Baca, Ed., *Introduction to Metadata: Third Edition*. Los Angeles: Getty Research Institute, 2016. [Online]. Available: <https://www.getty.edu/publications/intrometadata>

- [16] H. Herre, B. Heller, P. Burek, R. Hoehndorf, F. Loebe, and H. Michalek, "General Formal Ontology (GFO). A Foundational Ontology Integrating Objects and Processes: Part I: Basic Principles. Version 1.0.1," Research Group Ontologies in Medicine (Onto-Med), University of Leipzig, 2007. Accessed: Mar. 12 2025. [Online]. Available: <https://www.onto-med.de/sites/www.onto-med.de/files/files/uploads/Publications/2007/gfo-part1-v1-0-1.pdf>
- [17] A. Chang *et al.*, "BRENDA, the ELIXIR core data resource in 2021: new developments and updates," *Nucleic acids research*, vol. 49, D1, D498-D508, 2021, doi: 10.1093/nar/gkaa1025.
- [18] N. Kühl, M. Goutier, R. Hirt, and G. Satzger, "Machine Learning in Artificial Intelligence: Towards a Common Understanding," in *Proceedings of the 52nd Hawaii International Conference on System Sciences | 2019*, T. X. Bui, Ed., University of Hawaii at Manoa, Hamilton Library, ScholarSpace: Honolulu, 2019, pp. 5236–5245. Accessed: Jan. 22 2025. [Online]. Available: <https://hdl.handle.net/10125/59960>
- [19] Fraunhofer Institut für Produktionstechnik IPT, Vertrauenswürdigkeit schaffen für industrielle KI-Anwendungen. [Online]. Available: <https://www.ipt.fraunhofer.de/de/angebot/digitalisierung/ki/vertrauen-in-ki.html> (accessed: Jan. 22 2025).
- [20] N. Bäcker *et al.*, "Elaborating the potential of Artificial Intelligence in automated CAR-T cell manufacturing," *Front. Mol. Med*, vol. 3, 2023, doi: 10.3389/fmmed.2023.1250508.
- [21] D. Gurevitch, "Economic Justification of Laboratory Automation," *JALA: Journal of the Association for Laboratory Automation*, vol. 9, no. 1, pp. 33–43, 2004, doi: 10.1016/S1535-5535-03-00086-8.
- [22] B. Nießing, R. Kiesel, L. Herbst, and R. H. Schmitt, "Techno-Economic Analysis of Automated iPSC Production," *Processes*, vol. 9, no. 2, 2021, doi: 10.3390/pr9020240.
- [23] A. Elanzew *et al.*, "The StemCellFactory: A Modular System Integration for Automated Generation and Expansion of Human Induced Pluripotent Stem Cells," *Frontiers in bioengineering and biotechnology*, vol. 8, 2020, doi: 10.3389/fbioe.2020.580352.
- [24] B. Nießing *et al.*, "Automated CRISPR/Cas9-based genome editing of human pluripotent stem cells using the StemCellFactory," *Frontiers in bioengineering and biotechnology*, vol. 12, 2024, doi: 10.3389/fbioe.2024.1459273.
- [25] J. Ochs, F. Barry, R. Schmitt, and J. M. Murphy, "Advances in automation for the production of clinical-grade mesenchymal stromal cells: the AUTOSTEM robotic platform," *Cell Gene Therapy Insights*, vol. 3, no. 8, pp. 739–748, 2017, doi: 10.18609/cgti.2017.073.
- [26] F. Erkens, "AIDPATH - Modular Manufacturing Platform for AI-enabled hospital-based ATMP Production," 2022, doi: 10.24406/PUBLICA-338.
- [27] J. Krieger *et al.*, "Implementation of an Automated Manufacturing Platform for Engineering of Functional Osteochondral Implants," *Procedia CIRP*, Nr. 110, S. 32–35, 2022, doi: 10.1016/j.procir.2022.06.008.
- [28] F. W. Schenk, N. Brill, U. Marx, D. Hardt, N. König, and R. Schmitt, "High-speed microscopy of continuously moving cell culture vessels," *Scientific reports*, vol. 6, 2016, doi: 10.1038/srep34038.
- [29] L. Leyendecker *et al.*, "A Modular Deep Learning Pipeline for Cell Culture Analysis: Investigating the Proliferation of Cardiomyocytes," in *International Conference on Medical Imaging with Deep Learning, MIDL 2022*, 2022, pp. 760–773. Accessed: Jan. 22 2025. [Online]. Available: <https://openreview.net/pdf?id=hTil-xs1xNq>
- [30] F. Narrog *et al.*, "LIFTOSCOPE: development of an automated AI-based module for time-effective and contactless analysis and isolation of cells in microtiter plates," *Journal of biological engineering*, vol. 17, 2023, doi: 10.1186/s13036-023-00329-9.
- [31] F. Nienhaus, T. Piotrowski, B. Nießing, N. König, and R. H. Schmitt, "Adaptive phase contrast microscopy to compensate for the meniscus effect," *Scientific reports*, vol. 13, 2023, doi: 10.1038/s41598-023-32917-6.
- [32] J. G. Fujimoto, C. Pitris, S. A. Boppart, and M. E. Brezinski, "Optical coherence tomography: an emerging technology for biomedical imaging and optical biopsy," *Neoplasia (New York, N.Y.)*, vol. 2, 1-2, pp. 9–25, 2000, doi: 10.1038/sj.neo.7900071.
- [33] R. Wessels, D. M. de Bruin, D. J. Faber, T. G. van Leeuwen, M. van Beurden, and T. J. M. Ruers, "Optical biopsy of epithelial cancers by optical coherence tomography (OCT)," *Lasers in medical science*, vol. 29, no. 3, pp. 1297–1305, 2014, doi: 10.1007/s10103-013-1291-8.
- [34] M. Brehove *et al.*, "Cell monitoring with optical coherence tomography," *Cytotherapy*, vol. 25, no. 2, pp. 120–124, 2023, doi: 10.1016/j.jcyt.2022.09.008.

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