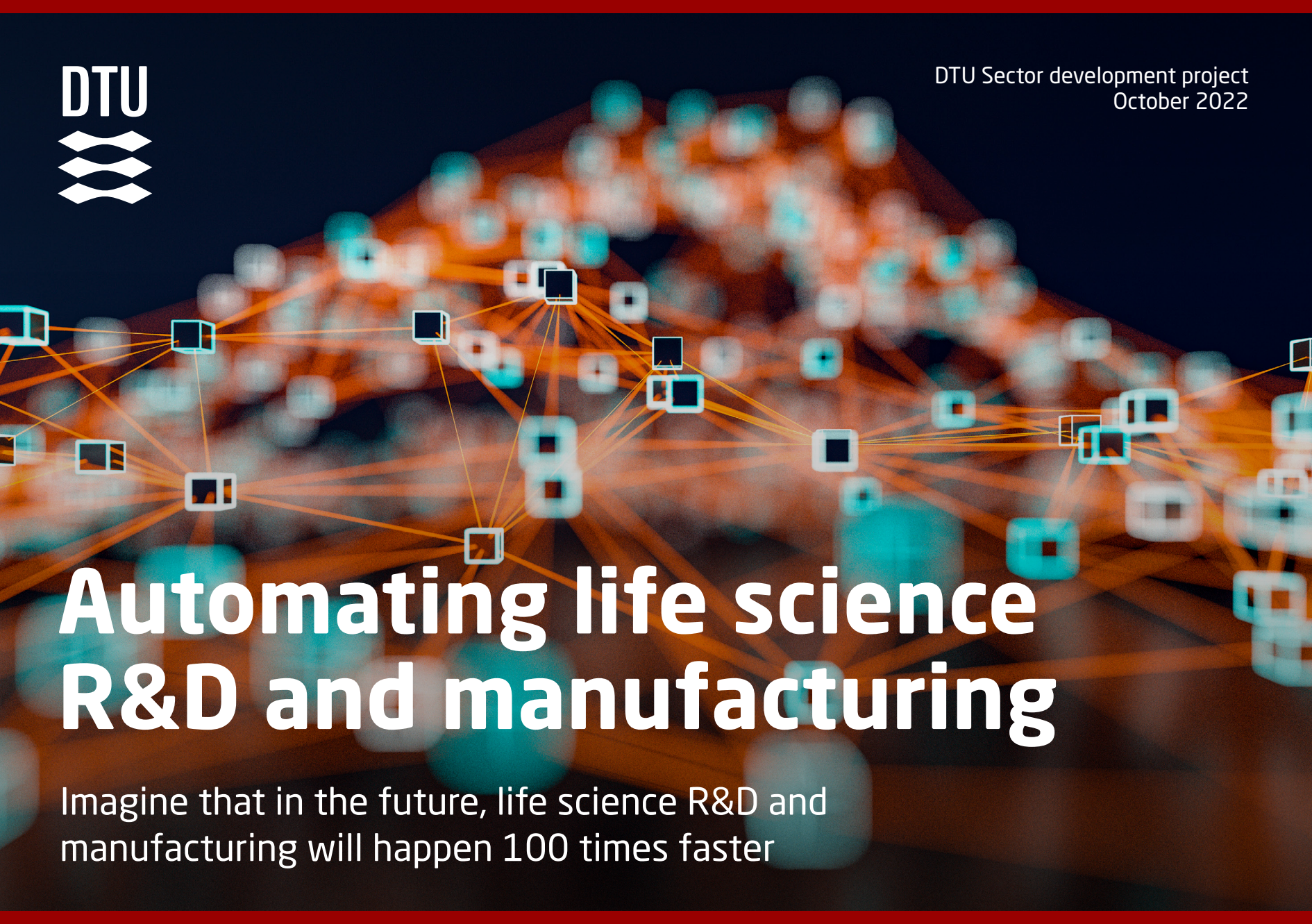
DTU

DTU Sector development project
October 2022



Automating life science R&D and manufacturing

Imagine that in the future, life science R&D and manufacturing will happen 100 times faster

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Preface

The Danish life science sector has delivered world-class performances over many years. However, a range of Industry 4.0 technologies, combining automation and digitalization, are globally sweeping across industry and society without having been fully implemented in life science.

This both presents an opportunity and a risk. On the one hand, we have the opportunity to harness these new technologies for optimizing production, cutting costs, and accelerating research, development, quality assurance, and time-to-market for new products. On the other hand, if neglected, competitors will fill the gap and undermine a core industry sector in the Danish economy.

Consequently, DTU has invited a range of industry partners, public institutions, and leading researchers to join forces with the purpose of creating momentum for automation and digitalization of the Danish life science sector.

The result is a list of recommendations and a roadmap for research, education, research infrastructure, and framework conditions – all necessary activities for the life science sector to keep a competitive edge. At DTU, we hope for a close collaboration with industry and public institutions aimed at putting the recommendations to work.

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The interviewed private companies, public institutions and trade organizations

Our approach

The main purpose of the sector development project is to identify the technological challenges companies face in connection with automation and digitalization within the life science sector. The project also aims to assess, which research is needed given the technological challenges, and thereby produce realizable visions for research and innovation in a 5-10-year perspective.

The work has provided insight into many challenges and opportunities associated with automation and digitalization. Together with companies, public institutions and authorities, and trade associations, we have identified research areas and framework conditions that can help create solutions that contribute to promoting automation and improving data utilization.

These were identified through interviews with key people from fifteen companies, public institutions and authorities, and trade associations. The results have been 'pressure tested' at a workshop attended by interviewees and at a steering committee meetings attended by the DTU department heads. In parallel with the interviews, workshops, and the steering committee meeting, the insights obtained have been discussed at monthly working group meetings for the participating DTU researchers. The project has been carried out with the participation of researchers from DTU Aqua, DTU Bioengineering, DTU Biosustain, DTU Compute, DTU Engineering Technology, DTU Chemical Engineering, DTU Chemistry, DTU Compute, DTU Construct, DTU Electro, DTU Engineering Technology, DTU Management, and a project manager from DTU CAS. Experts from the Danish Association of the Pharmaceutical Industry have contributed knowledge and input to the work. DTU Bioengineering and the Office for Research, Advice, and Innovation at DTU have coordinated the project. DTU is the report initiator. The recommendations in the report reflect the dialogue with actors from the sector and across the DTU departments involved.

Sector development project as a tool

Sector development projects are one of the tools DTU uses to collaborate with the business sector and the authorities. The aim of the projects is to improve the competitiveness of technology-intensive sectors by creating an overview and action plans for the development and use of new technologies in a 5-10-year perspective.

The method used:

- Mapping and analysing technology use in the sector via interviews and workshops
- Identifying bottlenecks and development needs – at companies, public authorities, and DTU (universities)
- Developing recommendations for research and framework conditions.

The sector development projects are created in a forum comprising representatives of companies, public authorities, and trade associations, in Denmark and abroad, and researchers from DTU.

Scope

The project has primarily been conducted from the perspective of users of automation technologies for R&D and manufacturing, while only limited input has been gathered from the producers of automation solutions. This deliberate take allows for focusing on user needs rather than on technology providers. However, the latter group will be instrumental for solving several of the identified challenges in the sector, such as the need for equipment interfaces standards, modular design of experimental designs and programming, as well as more efficient data flows.

The analysis does not include an in-depth assessment of the economic impact automation may have on R&D efficiency, for example, expressed as the R&D value per spend research funding. In part, this is due to a lack of data in this area, the unforeseeable changes in R&D behaviour automation brings, and the apparent difficulties of quantifying the actual value creation, e.g. knowledge or scientific insight in the long term. Similarly, the impact on material utilization, e.g., plastic ware and chemicals used for R&D, has not been analysed.

This is in part, because of the limited amount of scientific knowledge available within the area, the lack of knowledge regarding the non-linear relationship in the scaling of R&D process, and a lack of a common format for evaluating the sustainability within the sector.

Introduction

The opportunity

Denmark is in a unique position when it comes to meeting future life science challenges and addressing the associated markets. Several world-leading companies within biopharma, biotech, and sustainable industrial/environmental process design are headquartered in Denmark,[1, 2] and they are backed by strong research communities in academia.

By international standards, the Danish pharmaceutical industry measures up very well concerning export. Next to the Irish, the Danish pharmaceutical industry makes up the largest share of total exports in all EU-15 countries.[3]

Also, the development in productivity in the Danish pharmaceutical industry has been and is relatively high by international comparison. Only the Irish, Swedish, and Belgian life science sectors do better in terms of productivity levels, and the Danish life science sector has had the biggest growth in productivity from 2011 to 2018.[4]

However, this advantage cannot be taken for granted. In recent years, a range of technologies (collectively known as Industry 4.0) have been sweeping across several industry sectors: digital twins, artificial intelligence, Internet-of-Things, and flexible automation amongst others (Figure 1). Technologies that combined speed up research and potentially allow for the development of more advanced technological solutions than possible via traditional approaches. Currently, regulatory issues form one of the main obstacles within the pharma area that inhibits these technologies from entering the life science industry on a massive scale. Looking a little further ahead, however, there is no doubt that only companies which master the new reality will be the winners.

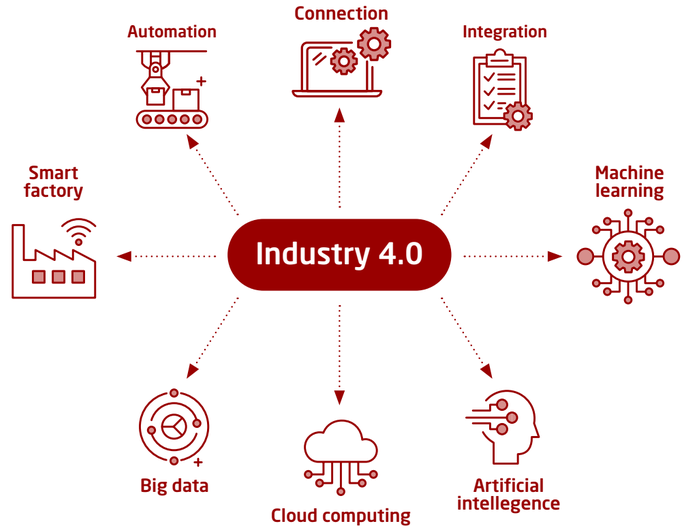


Figure 1
The Industry 4.0 concept that combines a series of separate technologies, has successfully been implemented in sectors such as the semiconductor and car manufacturing industries, resulting in development cycles, reduction of costs, and more agile production. The life science sector (pharma and biotech) could obviously benefit from the Industry 4.0 approach, yet its implementation has proven difficult – but why?

Faster time-to-market

Again, the good news is that Danish research is at an advanced level in all the relevant Industry 4.0 disciplines: robotics, Big Data, AI, data science, etc. However, the bad news is that these competences are currently poorly integrated into life science. This is perhaps not surprising, since the life science industry – with some exceptions – only very recently have recognized the advantages that automation and an increased focus on data analysis bring, meaning that it is now becoming an outspoken and widely recognized strategic priority. Consequently, the workforce and researchers within the sector lack relevant cross-domain knowledge and the ability to combine the disciplines necessary to implement an industry 4.0 approach.

This situation must change, not least since life science automation will reduce the time-to-market, and potentially allow R&D to produce better solutions. Both key for efficiently addressing the pressing societal challenges, as outlined by the UN Sustainable Development Goal (SDG's) and pandemic-type threat. Specifically for the pharmaceutical industry, a significantly faster time-to-market for vaccines and new pharmaceutical treatments is highly realistic. A key limitation for time-to-market is the artificial organizational separation of R&D and manufacturing (Figure 2) found in most organizations. It results in R&D developing products not with the 'end in mind' and thus violating hard constraints downstream on the manufacturing side: a key realization here is that fundamentally biologics and other relevant products developed in R&D are ultimately the same entities that need to be produced, quality controlled and shipped at scale. This should motivate a more holistic take on the whole life science value chain and automation of operations, with data processes potentially being the change driver for this undertaking. Further, this industry will be able to substantially increase productivity through much higher efficiency in the R&D and CMC[5] processes. Importantly, this not only holds true for new products, but also for established brands. For Denmark to remain competitive as a host country for pharmaceutical and biotechnological manufacturing, the efficiency relative to costs needs to be among the best in the world.

Moreover, for the biotech industry, it is important to understand that automation is not so much about making current processes more efficient. Rather, automation should be seen as a vehicle for innovation, an opportunity to efficiently search for larger solution spaces to reach superior technological solutions based on increased insight offered by AI-based analysis of larger high-quality datasets. A key part of biotech R&D (and pharmaceutical R&D) is the screening of large libraries of related molecules or cell factories. Often the sheer cost of this exercise will inflict limitations, but if efficiency and throughput can be maximized at low cost, the chance of finding the right molecule for a given task becomes much higher.

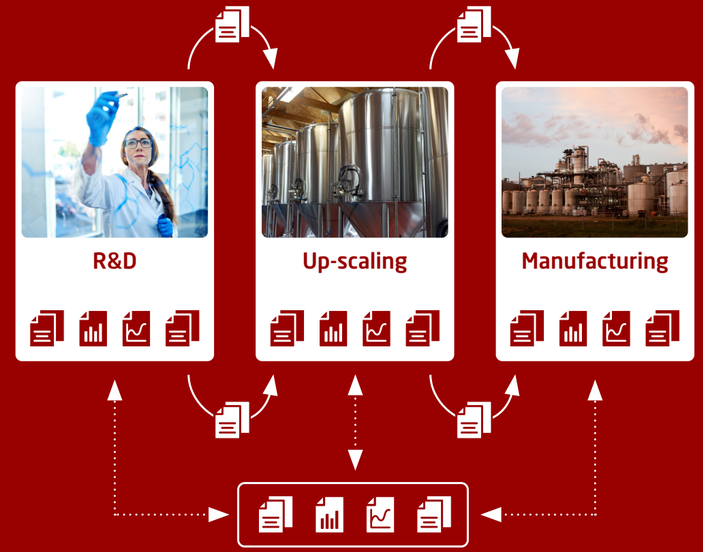


Figure 2
Innovation/product development flow in most pharmaceutical and biotechnology companies. Upper panel: Projects are typically handed over from R&D to upscaling to manufacturing via a gated process, often resulting in a unidirectional information flow where only a selected set of data and experience are moved from one step to the next. Lower panel: Integrative information flow where handover reports are accompanied by access to all data generated in the company, allowing for example the early R&D team to gain an understanding of what worked at full scale manufacturing.

Novozymes

Intuitive interfaces pave the way for automation

According to Senior Director Anders Viksø-Nielsen, Novozymes R&D, life science automation is currently at a crossroad:

"Given the technological progress in recent years, the main barriers are now on the employee side. People have their routines and may not always see the advantages of automating. In some cases, typically when we are talking about small batch sizes, a robot will not be able to perform a given task faster than a human. However, speed is not the only relevant parameter. Since a robot can work 24 hours a day, we achieve a significant increase in capacity whenever we can automate a process. Further, we will be able to transfer the employee to tasks which are more fulfilling, less tiresome, and generate more value for the company."

Further, it may soon become rational to automate even small batch size processes:

"We see a strong development within user interfaces. Previously, as you would need to spend some time for programming the robot, automating small batch size processes quickly became uneconomical. But now the interfaces have become very intuitive and easy to use. Also, you don't need to know actual programming any longer. This widens the range of employees who can operate the robot."

To Anders Viksø-Nielsen, automation is not optional:

"If we want to stay competitive in Denmark, there is no alternative to automation. Since wages are much lower in many other countries we need to be among the best in productivity per employee. Further, automation is not only about improving productivity. The future belongs to companies which can use, for example, machine learning and similar tools to continuously improve their processes. For this to happen, we will need to apply integrated automation and digitization, ensuring that process data are automatically harvested into a designated data warehouse."

How far has Novozymes come in this regard?

"Well, some areas within the company are very advanced, others less. I believe that a higher level of standardization could move things forward. Notably, this should not be just within Novozymes. The value would be higher if we could have genuine industry standards for the sector."
"In any case, I can say that things are moving in the right direction. For instance, ever more often we will hire a data scientist for an R&D position rather than a chemist. As a rule of thumb, we strive to have a 1:10 ratio of data scientists relative to chemists. It is healthy to get a different mindset represented when you want to automate."

A further barrier, however, is the background of the candidates:

"How to automate life science processes is just not something you are taught at universities – not yet at least. Ideally, we would like for our new employees to hit the ground running, but currently that is not the reality in this field. Most often we must train new employees quite extensively. It would be great if more candidates with a knowledge of both life science and automation were available."

Data-driven R&D, manufacturing, and quality assurance

Through the present sector development project, DTU has invited a range of industry partners, health care authorities, and leading researchers in relevant fields to join forces. The obvious goal is to create a momentum for automation and digitalization of the life science sector.

A key insight from the project is the fact that as the life science sector differs from many other sectors by its high focus on research and development, only automation that addresses both R&D and manufacturing will be truly successful.

Especially for the pharmaceutical industry, automation across R&D and manufacturing is particularly challenging. While R&D needs to have large scope for creativity and experimentation, manufacturing of pharmaceuticals is for obvious reasons subject to rigid regimes. Still, merging these two very different phases of the product development cycle in life science domains is the task. On the upside, the exercise also promises to benefit the industry's third pillar, quality assurance (QA): if well designed, the data generated in fulfilment of the R&D and manufacturing processes demand can be directly applied in QA. This, however, will only yield the optimal benefits through modification of current health authority regulations. If industry needs to run a data-driven and an analogous QA in parallel, nothing is gained.

The scientist robot: introduction of AI and automation-driven product discovery and hypothesis generation and testing

Here, the 'the robot scientist' refers to automating both the scientist's cognitive tasks and experimental workflows in life science R&D (Figure 3). While this might sound like science fiction, proof-of-concept exists in the form of 'Adam the robot scientist'[6],

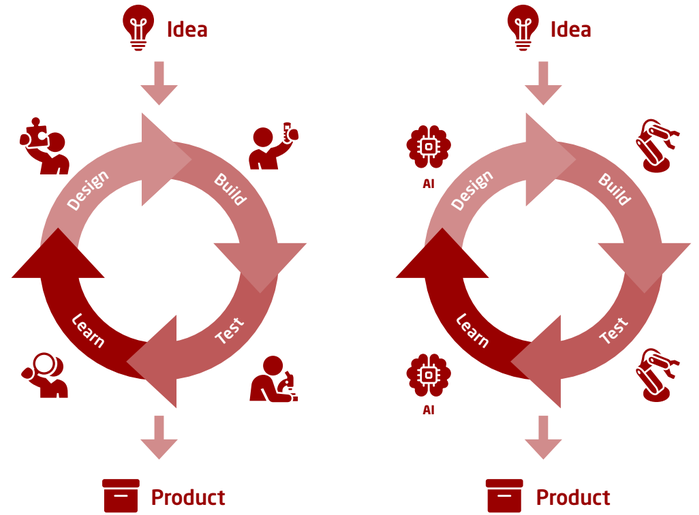


Figure 3: R&D/innovation cycle
Left: The workflow in most life science organizations, both public and private, where humans generate the ideas/hypothesis, build and test the solutions, and interpret the results to generate new innovation/hypothesis. Right: the future workflow where many of the steps are either taken over by, or assisted by, robotic and AI-based analytics and decision-making. The latter solution is dependent on automation, standardization, and a strong underlying data structure to allow for automation of the computational/cognitive steps (learn and design steps).

a fully automated robotics set-up that carried out hypothesis-driven functional genomics research in Yeast and first machine in history reported to have discovered new scientific knowledge independently of its human creators (there exists also "Eve"[7] now, conducting independent drug discovery research).

Furthermore, significant advances in AI, in particular deep learning, have revolutionized several scientific and engineering domains, including speech recognition, image recognition (including object detection), and natural language processing (LeCun et al. 2015).

Within life sciences, the application of deep learning in the form of AlphaFold has largely solved the problem of protein structure prediction – a problem so challenging that few expected it to be solved anytime soon – vastly outperforming all state-of-the-art methods developed so far. In its short existence (published July 2021), AlphaFold had a large impact on biological research as is reflected by the extreme number of citations the manuscript has accumulated already (1839 citations on May 25). Importantly, development of AlphaFold was dependent on decade-long input from experimental scientists (protein structures) and a well-defined data-structure to allow for training of the AI. With the help of automation, similar large and high-quality datasets will become available to efficiently train AIs with the potential to revolutionize many other areas within life science.

A combination of AI and automation thus holds a big promise for vastly improving product discovery (drugs, enzymes, fuels, meat alternatives, etc.) as well as hypothesis-driven research (e.g., for identifying mode of action of a drug necessary for FDA approval).

Improved ergonomics as a powerful argument

Another insight relates to the human factor. A general observation across many types of technological transformation is the importance of employee knowledge, knowhow, and motivation. In the case of life science sector automation, a lack of knowledge and knowhow about how to programme, operate, maintain, and repair robots, design optimal automated workflows, and conduct Big Data analysis form an impediment to change. In addition, transformation can sometimes challenge employees' motivation. Here, a powerful argument for motivating employees for life science sector automation is improved ergonomics. Many processes such as pipetting in R&D and packing in manufacturing involve tiresome repetitive labour. If designed properly, automation will both improve the physical work environment and allow for more fulfilling job content (Figure 4).

Moreover, the project points to benefits, which cannot be detailed in advance. Experience across many industry sectors suggests that once companies begin automating and digitizing their R&D and manufacturing, new insights will transpire. We have every reason to believe this will happen in the life science sector as well. While the high complexity involved in biological manufacturing makes automation challenging, the very same complexity practically guarantees that machines can detect patterns and solutions that lie beyond the sight of even the most skilled human experts.

In conclusion, the current state of automating life science R&D and manufacturing is a ripe opportunity for developing new technologies that go far beyond the implementation of existing solutions. It is also a huge practical challenge that can only be addressed by a truly cross-disciplinary effort, bridging classical engineering for robotics with that of biology and chemistry. If neglected, it is a significant threat, since competitors elsewhere may soon fill the gap and thereby undermine a core industry sector in the Danish economy.

Figure 4
Collaborative robot (Cobot) already assist humans in manufacturing workflows in, for example, the electronics industry to reduce the repetitive work performed by workers to protect them from developing occupational injuries.

Definition of automation in the life science sector

Our definition of automation broadly encompasses the utilization of both hardware (e.g. automated liquid handlers, industrial robotics), software (e.g. robotic process automation (RPA)), and AI (e.g. Bayesian optimization) technologies to automate and replace both manual labour and decision-making for the purpose of improving life science R&D and manufacturing processes across their complete value chain (see Table 2 for the many different forms of value provided by automation).

Forms of value added by automation to R&D and manufacturing in the pharmaceutical and biotechnology industries.

Common benefits that automation provides to both R&D and manufacturing:

R&D/manufacturing throughput and efficiency:

a. Liquid handling workstations and other lab automation solutions can operate 24/7, facilitating a throughput of data generation that is difficult to impossible to achieve with manual processes. This leads to a reduction in time to market and a diversification of product portfolios (as more product leads can be pursued simultaneously).
b. Manufacturing processes are dominated by less than fully efficient batch operations in part due to the involvement of a human work force. Rolling out automation on the production floor will facilitate the adoption of continuous manufacturing operations and thus the desired throughput and efficiency gains.

Ergonomics & safety: repetitive strain injuries caused by manual experimental work (pipetting, microscopy, cleaning, lifting etc.) are a huge ergonomics concern for the laboratory scientist and technician workforce with 46.5% of lab technicians having the same work position 25% of their workdays and 32.8% of them experiencing arm pain several times in a work week[8]. Furthermore, dangerous operations that are currently carried out manually on the production floor can be carried out with robotics leading to safer work environments.

Data governance: several factors contribute positively to an improved reproducibility of life science experiments, which is a big concern in both academic and industrial research:

c. Accuracy and elimination of human error: generally, the accuracy of liquid handling workstations is much better than that of human operators (in terms of coefficients of variation) leading to a significant reduction of noise in the experimental data generated. Furthermore, human errors are reduced by automation, again leading to a reduction of noise and outliers in the data.
d. If integrated with a LIMS (laboratory information management system), laboratory automation can facilitate the automatic tracking of materials processed providing a complete experimental track record. This significantly reduces the burden of manual data entry into ELNs/LIMS and simplifies the diagnosis of problems in experimental workflows. Importantly, it also facilitates the automation of data handling and processing. On the manufacturing side, it is also an essential requirement for GMP.

Benefits that automation can provide to life science R&D:

Opportunity cost reduction: time saved on performing manual procedures in the lab can be invested more productively: (i) researchers can spend their time more effectively on data analysis and interpretation leading to better planning, writing and innovating and (ii) laboratory technicians can spend more time on data handling and processing and the development of new assays and experimental procedures.

Experiments that are only feasible due to automation: typically, randomization (reducing confounding factors, e.g., positional effects on a microtiter plate) and Design of Experiments (enabling the efficient exploration of large search spaces, e.g. for assay optimization involving multiple parameters) are not utilized in manually carried out experiments. The reason for this is that these approaches necessitate complex, cumbersome, and error-prone single-channel pipetting steps but laboratory scientists and technicians rely very much on multi-channel pipettes to achieve the necessary experimental throughput. Automatic liquid handling stations do not have these issues.

Benefits that automation can provide to life science Manufacturing:

Improve fidelity in manufacturing: the introduction of automation in manufacturing set-ups reduces the risk of operator caused errors, which is a real problem in the highly regulated pharma area.

Automation will allow for a more detailed monitoring of diagnostic parameters in production lines, providing better datasets for decision-making, and reducing the downstream quality control task.

The scope of the sector development project.

The scope of the project is automation of R&D processes and diagnostics in the lab and of manufacturing processes within the life science sector. Both biotechnology and pharmaceutical companies (SMEs and LEs) are within scope of the project, and their complete value chains are considered ranging all the way from early-stage R&D (including target discovery and identification), CMC/scale-up, filling and packaging, to the consumers/patients. Medical devices, digital health, and food processing companies are not. It also addresses the implications of increasing automation on life science work environments, barriers in work culture that need to be overcome, and necessary upgrades of life science education.

New players take stage

As new technologies for life science automation emerge, so does a range of start-up companies offering automated laboratory services, ranging from stand-alone analysis to complete project flows. The following examples showcase some of the significant new players on the international scene, and their focus.

Gingko Bioworks

USA-based Gingko Bioworks develops solutions in strain improvement, enzyme discovery, biosecurity, mammalian cell engineering, and related disciplines.

The company website features an illustrative case: "Strain engineering often requires improving production hosts. In one such instance, out team sought to modify our partner's heavily engineered E. coli strain. This strain already expressed seven enzymes to produce their target molecule (..). Our campaign began by integrating multi-omics data sets. Our systems biology team used untargeted metabolomics to construct a metabolic model. We then used RNA-seq transcriptomics to identify differentially expressed genes. The data from this work defined a set of more than 300 genes predicted to impact the production of the target small molecule. We designed more than 3,000 genome edits that modulate expression of native E. coli genes and applied these to a previously engineered production strain (..). The workflow resulted in a total of 144,000 mass spectrometry data points and identified more than 100 candidate strains with significantly improved titers in small-scale cultures. The engineering campaign from design of DNA to generation of screening data was completed in approximately three months."
https://www.ginkgobioworks.com/

Strateos

Established in 2012, USA-based Strateos is – according to its own webpage – "the world's first automated R&D robotic cloud lab and private lab control software platform." Further, the company mission is "to create new knowledge driven by data, computation, and high-throughput robotics with the goal of fundamentally advancing the life sciences."

Again, according to the company, users of Strateos remote labs see big savings. The automated workflows reduce hands-on operator time by about 90 % on average. A high-throughput screening solution allows screening over one million small molecules in 15 days.
https://strateos.com/

Actoris

Actoris is a drug discovery company headquartered in Oxford and Boston. The company uses advanced cellular and molecular biology techniques on an automated platform to validate novel targets. Quoting the Actoris homepage: "We deploy both the latest in silico and well-established in vitro screening approaches (..). This unique pairing of computational techniques (virtual screens, ML-guided molecule selection) and wet lab automation generate high quality hits faster and more efficiently."

More specifically, the homepage outlines the services of Actoris: "Machine learning guiding screening set selection and hit evolution. In silico screening, docking and molecular dynamics. In vitro screening and profiling from as few as five molecules (for deep mechanistic studies) to full HTS (100k+ compounds). Curated and focused libraries. Compatibility and management of third-party and custom libraries. Biophysical screening/profiling and fragment-based drug discovery. Phenotypic screening by single molecule and synergy matrix screens, cell panels, and cell viability/cytotoxicity assays."
https://www.arctoris.com/

Edinburgh Genome Foundry

EGF (the Edinburgh Genome Foundry) is a research facility within University of Edinburgh. EGF specializes in the assembly of large DNA fragments using a highly automated platform.

Quoting the EGF homepage:
"We build genetic constructs for academic and industrial customers to equip cells or whole organisms with new or improved functionalities. We work on projects as diverse as programming stem cells for use in personalized medicine, vaccine development, gene therapy, living biosensors, and optical tools for basic biological research (..). We deliver high-throughput projects involving long constructs (larger than 5 kbp), constructs comprising large numbers of genetic parts, or combinatorial libraries. Our platform is agnostic on the host chassis; to date, we have assembled constructs for use in bacteria, yeast, and mammalian cells."
https://www.ed.ac.uk/biology/research/facilities/edinburgh-genome-foundry

The history

The history of automation in the life science sector

R&D

There is a long history of laboratory scientists developing bespoke DIY automation solutions to increase their experimental throughput and reduce repetitive tasks. Examples for this include automated filtration devices and siphons developed in the late 19 century[9]. After World War II, commercial solutions emerged, for example, the AutoAnalyzer I[10] in 1957 that automated standard medical laboratory analyses.

In the 1980s, the need to assess the activity of large libraries of natural products (10,000-100,000s) led to the development of high-throughput (HT) screening in pharmaceutical drug discovery at companies such as Pfizer[11]. HT screening involved the development of automated liquid handling and the broad adoption of standardized laboratory consumables, such as the microtiter plate, a flat plate containing multiple wells that replaced test tubes. Which was originally developed in 1951 by the Hungarian medical doctor Gyula Takátsy to facilitate high-throughput laboratory testing of influenza virus infections.

The development of the thermocycler for automating the Polymerase Chain Reaction (PCR) procedure was another breakthrough giving rise to modern day biology. Previously conducted by molecular biologists moving test tubes back and forth between differently tempered water baths, a controllable heating block could cycle efficiently through determined temperature ranges to amplify DNA.

Since the 1980s, however, the development of laboratory automation technologies has essentially stagnated, still finding its main use in HT screening and specialized devices.

Manufacturing

Over the last three centuries, the manufacturing of pharmaceuticals and bio industrials has evolved from small-scale manufacturing, involving the manual processing of materials using hand operated tools, to the present large-scale production of a trillion-dollar industry.[12]

Beyond filling and packaging (which are governed by conventional robotics solutions), however, the pharma and biotech industries have been slow in the adoption of automation in other areas of their manufacturing value chain. In pharma, progress has been slow due to GMP regulations and a risk awareness

Sector analysis

The Danish pharmaceutical industry is one of the most important industries in Denmark, when measured by its exports (136 billion Danish kroner, 19.5% of all exports), which by far exceeds the exports by most other export intensive industries in Denmark.[13] In addition, by international standards, the Danish pharmaceutical industry measures up very well concerning export. Next to the Irish, the Danish pharmaceutical industry makes up the largest share of total national exports in all EU-15 countries.[14]

Measured by job creation the Danish pharmaceutical industry is growing in significance for the Danish economy. In Danish industries at large, employment in industry has decreased by 25% since the year 2000. In the Danish pharmaceutical industry, employment has increased by 122% in the same period.[15]

Consequently, a relatively large share of the Danish work force is employed in the life science sector as compared to neighbouring countries. In fact, in Denmark the largest share of the work force in general is employed in the pharmaceutical and biotech industry.[16]

The job creation results from very high annual growth in value creation. The life science Sector share of the overall national value creation in Denmark surpasses the share in many other EU countries.[12]

In addition, the job creation is a result of a relatively high development in productivity in the Danish life science sector compared to in other EU countries. Only the Irish, Swedish, and Belgian life science sectors do better in terms of productivity levels, and the Danish life science sector has had the biggest growth in productivity from 2011 to 2018.[17] What has made the Danish life science sector do so well in export development, job creation, value creation and productivity?

For one, the Danish pharmaceutical industry each year invests in the range of DKK 10-12 billion in R&D processes. In fact, the Danish private investment in the R&D processes in the pharmaceutical industry is next to the Swiss private investment the biggest among all countries.[18] Secondly, and in part following from the investments in R&D processes, the Danish Life-Science industry in 2019 submitted more patent applications per capita to the American and European patent offices than each of the American, German and Chinese industries did.[19]

Thirdly, with 37 clinical trials per 1 million capita, Denmark is by far the country in EU-15 with the most clinical trials. Belgium comes in second with 31 clinical trials per 1 million capita. Looking only at industry-financed clinical trials, Belgium is the leader with 26 clinical trials per 1 million capita in EU-15. Denmark comes in second with 22 industry-financed clinical trials per 1 million capita[20].

Together, the relatively high investments in R&D processes and relatively high number of patent applications, and the relatively high number of clinical trials help the Danish pharmaceutical industry develop competitive products and do it at a relatively fast pace.

Pace matters. The market introduction time of new prescription medicines has decreased ever more over the course of time from 10.3 years in the 1970s to just 2.3 years in 2005-2011.[21] This development naturally puts a growing pressure on pharmaceutical companies to increase the effectiveness of R&D, CMC[22] and manufacturing processes.

Therefore, automation of R&D and manufacturing processes has become increasingly important in the latest years.

The question is if the Danish life science sector is up and ready to get the job done.

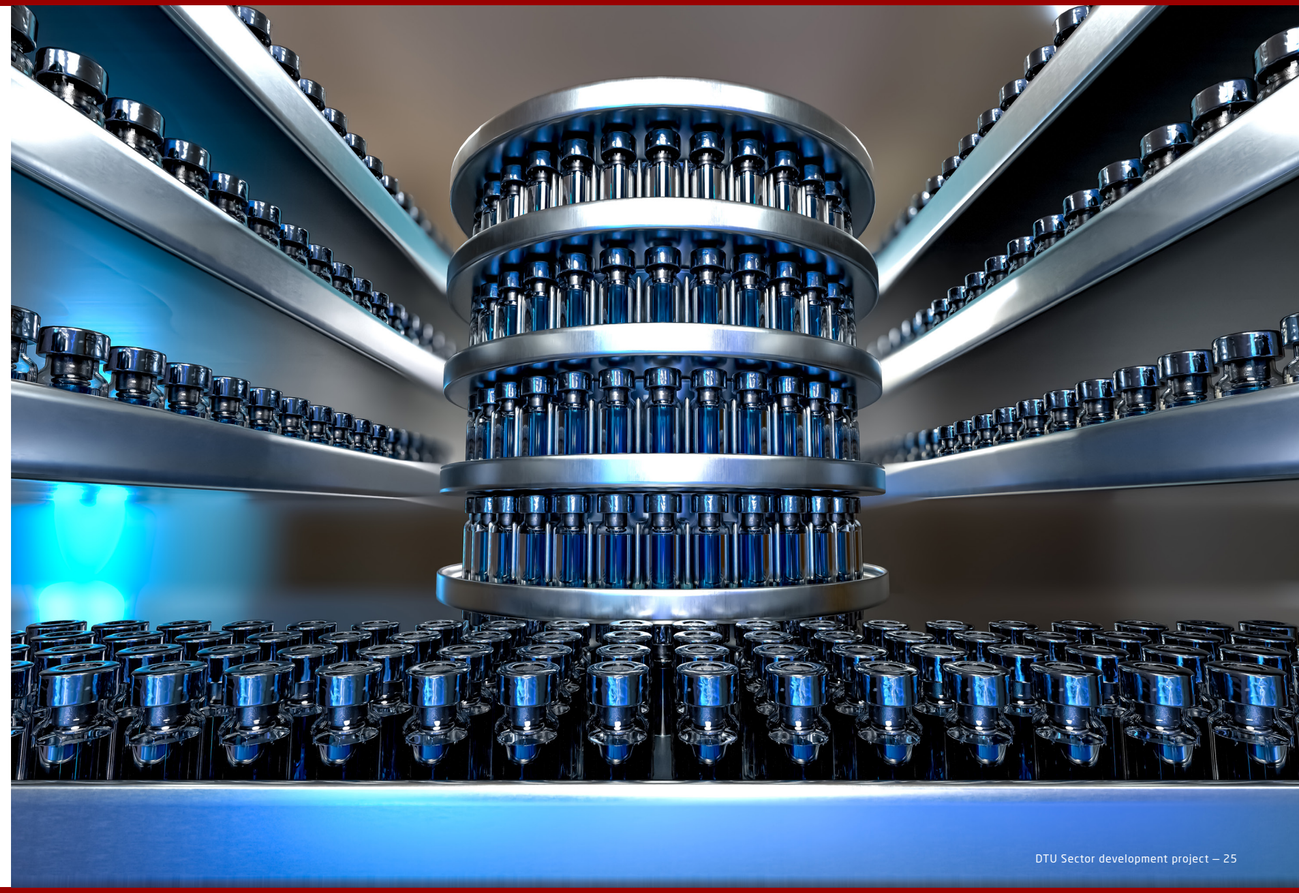
Diagnosis of sector

Arguably, there is a need for automation in the Danish life science sector.

Automation of manufacturing processes seems to be especially urgent relative to automation of R&D processes. According to the interviews conducted in the sector development project with the private companies, they identify more forms of value added from automation of manufacturing processes than of R&D processes.

Automation of the documentation processes associated with CMC seems to be a somewhat overlooked opportunity, considering its relative significance to other business processes in the life science sector.

The learning curve for automation appears to be very steep among the private companies. Possibly, only one or two of the private companies have an outspoken strategy for automation and are mobilizing resources and re-organizing for automation. The rest are working hard to become fast followers. Overall, the sector lacks behind in the use of automation relative to other industries that are usually not considered as high-tech as the life science sector.



One major reason is that most life science companies do not yet hold all the relevant competencies and do not master the individual technologies needed for automation to become a real opportunity for business development.

For one, life science companies (still) struggle with structuring their internal data and getting it ready for use across internal sections (manufacturing, CMC, R&D, businesses, and IT sections) within the individual company and for use with data located outside the private company's administrative barriers. Secondly, the various technologies needed for automation are not yet widely employed together in the manufacturing facilities and R&D departments in the private companies. The same applies to the ergonomics and human factors side in terms of their use and effectiveness.

Another explanation lies in the composition of the private sector workforce. Few employees have so-called T-shaped skills profiles[23], which on the one hand are in-depth specialized and on the other hand encompass a broad knowledge of neighbouring fields, allowing them to serve as gatekeepers for automation projects. The companies hence struggle with getting people across these disciplines to work together. Whether the optimal gatekeeper would be a professional specialized in digitalization, or a professional specialized in synthetic biology/biotech remains unclear. In any case, the gatekeepers need to possess a combined understanding of molecular biology and computer/electrical/mechanical engineering, thereby bridging experimental biology and computation/automation (Figure 5). In addition, they need to possess an understanding of the possibilities and limitations of the automated life science domain. This understanding would allow the gatekeeper to devise realistic high-level strategies within the automation and digitalization area and efficiently collaborate with both within the biology and automation domains.

In addition, when attempting to explain how an industry fares in its use of a specific set of technologies, one also needs to consider the framework conditions. In the case of the pharma sector, the European Medicines Agency, the U.S. Food and Drug Administration, and the Danish Medicines Agency form and regulate the framework conditions. For very good reasons (documentation of/security for efficacy, safety, and cost-optimization) the agencies uphold a regulatory regime that keeps data safety standards very high. The implication of this for any relevant data (its production, storage, and distribution) is that the storage and distribution of data in the cloud etc. is something that the agencies cannot accept. This, whilst important, substantially hampers the unlocking of the full potential of digitalization for automation within the life science sector.

Lastly, but not least, the life science sector is, as things stand now, not supplied with the sort of gatekeepers identified above. For example, universities because of both self-imposed and externally imposed incentive structures struggle to educate young people that possess T-shaped skills. Therefore, the life science sector is currently not in the position to recruit people with these competencies.

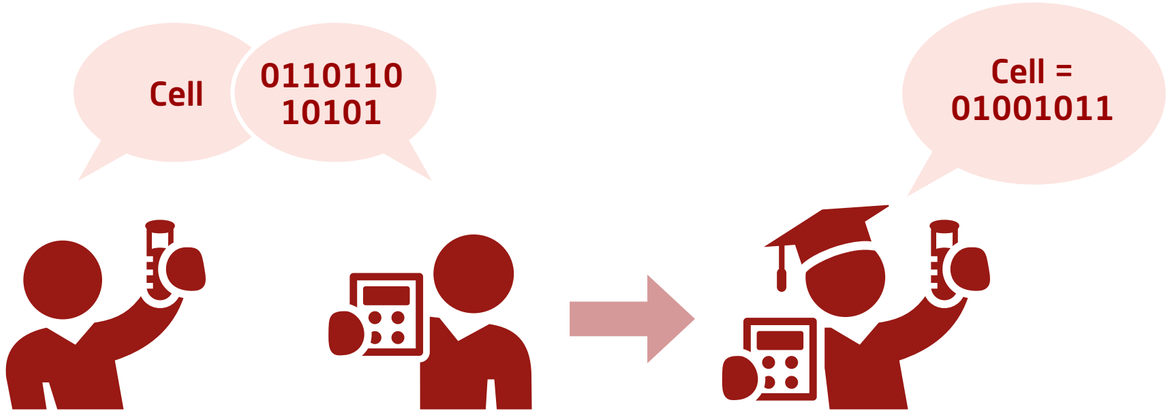


Figure 5
Communication across the required disciplines is often a major barrier for successful implementation of automation solutions in life science – experts use domain specific language. Ideally, the future workforce have T-shaped skills, or a bilingual, bridging the life science, robotics, and computational domains.

XX Company[24]

According to a principal automation scientist in a multinational pharma company, the sector needs to adopt automation at a much higher pace than is currently seen, at least for R&D:

"Very few companies in the life science-based industry have a strategy for automation. Okay, for small young companies in the biotech sector, available funding for the purpose is typically scarce, and it may not make much sense to have a strategy. But even companies which have the money to make things happen most often don't have a strategy. The main cause is lack of automation expertise at the top level and a tendency to rely on individuals in the organization taking on the field out of their own drive and initiative"

"For the same reason if you are passionate about automation and you have the mandate to go ahead, you shouldn't wait for top management to ask you to get started. Don't wait for requests!"

The automation advocate should take a pragmatic approach to achieve an "Automation Mindset":

"Some people think 'bigger is better'. They purchase something large and expensive and expect it to run by itself. When that doesn't happen, you end up in a scenario with a few employees becoming experts on the solution while the rest are, in fact, afraid of it. Instead, my advice would be to start smaller. Buy a limited solution and train all relevant staff to get hands-on routine with the system."
"In this way you can scale up and slowly build a proper automation mindset. When that happens, it's fantastic. You will have people coming to you with ideas of more processes which could be automated."

Still, an automation strategy and money are not enough. A company will also need people with the right background:

"This is where things become very difficult. Since in the life science industry we work with living organisms and/or chemical reactions that we automate, we face multiple limitations which don't exist in other industry sectors. An automation solution is useless if the biology is killed somewhere along the way. Therefore, you cannot hire for example an electrical engineer to do the job. On the other hand, most experts in the biological disciplines have no understanding of automation and digitalization."

"Ideally, you should hire candidates with a deep understanding of all the very relevant disciplines plus what you might call translational skills. However, that would require people to exit university with 20 years of experience in a number of translational fields. Of course, this is not realistic. I don't know of any magic bullet which can solve this dilemma."

Still, according to the principal automation scientist universities have a chance to build candidates better suited for the reality of a new type of work environment including automation:

"Ironically, when someone new joins the workforce in R&D here in 2022, there´s a clear understanding that their work will entail using handheld single-tip pipettes (invented in the 50s) but usually not that they will be using automation. Would be nice if freshly educated colleagues had at least an awareness of automation and digitalization when they enter the work market."

"In any case, I strongly believe that we as an industry face a point of urgency. The demand for automation is not a thing of the future, it's here, and it's going on right now! The earlier we start to adapt to this reality, the better our chances will be."

22. The company name has been anonymized for reasons of confidentiality.

The basic model concept

The basic model of a cross-disciplinary research profile concept

Through the sector analysis, we have identified the need for a cross-disciplinary research profile, for which we have devised a basic model (Figure 6). The basic model puts forward the overall objectives, principles, and means of, how to succeed in developing solutions for the challenges the sector faces. In essence, guided by overarching principles and a holistic view on life science automation, the research profile will provide a comprehensive toolbox that will enable researchers to mix and match the right tools and competences for the challenges at hand. The key research questions addressed by the research infrastructure will focus on how to connect technologies and knowledge from distinct fields and industries.

It will also provide the cross-disciplinary and research-based teaching environment for a novel life science automation education that fosters the development of employees with 'T-shaped skills', i.e., individuals that combine deep knowledge and skills in one domain with the desire and ability to connect the dots across disciplines, through primary and continuing education.

Guided by overarching principles that provide a holistic and human centric view of the life science sector, the cross-disciplinary research profile combines technologies and research from distinct fields to develop novel and innovative solutions for challenges that come from across the whole value chain of pharma and biotech. The objective is to help make R&D and manufacturing more efficient and better integrated, which will offer a substantial contribution to the digital transformation of these industries.

Objectives (aim)

The transition to automation and data-driven design/operations in the life science sector provides the means for improvements in R&D and manufacturing: The primary gains within R&D will be improved data quality, increased throughput, reductions in costs, and improved ergonomics for the persons involved. The increased data quality will facilitate advanced data analysis techniques, such as machine learning, maximizing learning from experiments. The gains within manufacturing will be more efficient production. The transition towards automation also provides the means for integrating R&D and manufacturing areas better, which presently are two separate worlds. Finally, facilitating a high degree of automation is also an objective.

Principles (mindset)

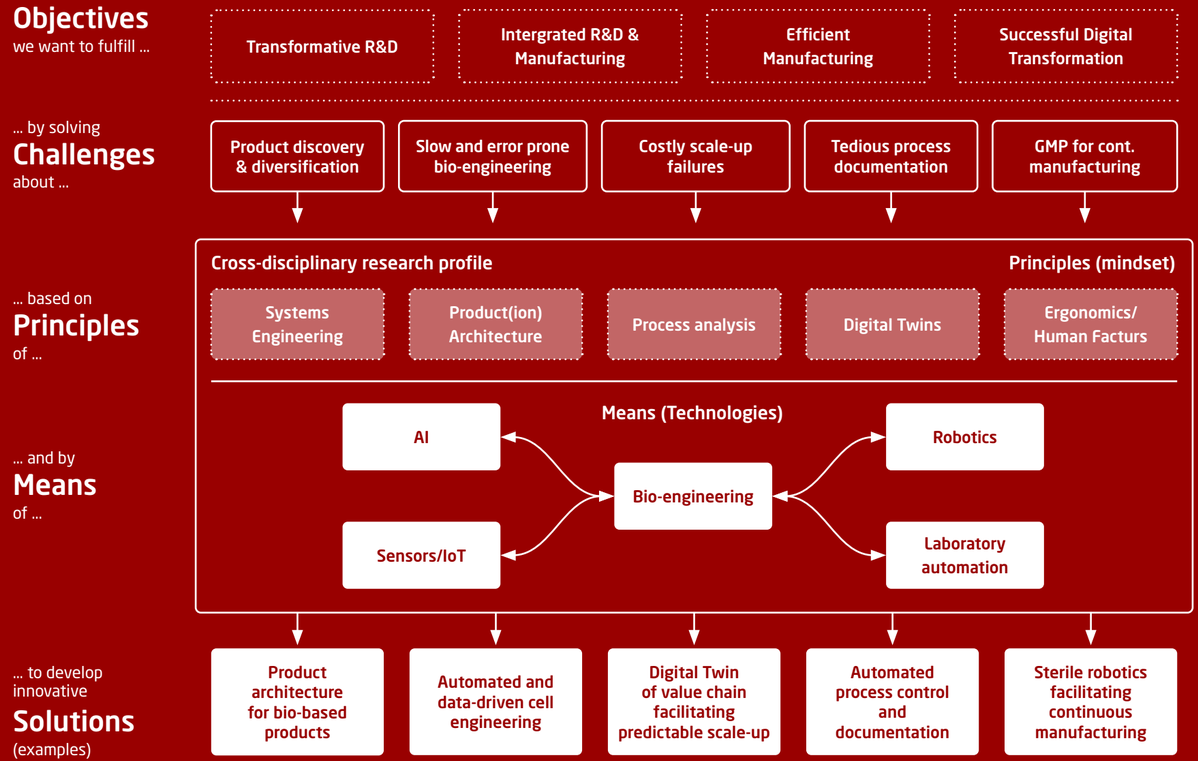
The overarching principles and methodologies of the cross-disciplinary research profile include systems engineering, process analysis, product and production architectures, and Digital Twins. Together, they will provide a holistic and human-centric view of the sector: Systems engineering and process analysis will facilitate the systematic modelling of the whole R&D and manufacturing value chain.

Developing product and production architectures will help determine standards, interfaces, and constraints for both bio-products and their production, simplifying the development of new products and facilitating a rapid expansion of existing product portfolios. Digital Twins of the whole value chain will provide a virtual playground for new solutions

to be tested in the broader context of automation and provide the means for systems level planning and collaboration. Lastly, the consideration of Ergonomics and Human factors in the context of management practices will ensure that the solutions developed take a human-centric approach that will facilitate adoption and change management. In particular, the human-robot interaction needs to be designed so that the 'collaborative' assumptions of the human-robot interaction are explicit and well thought out from the perspective of wellbeing, including the extent of control a person has over the operative system. Beyond ergonomics, it is important to consider continuous improvement: how does the automated system as a whole learn and improve? How are the ideas for improvement programmed into the system? It is also important to assess the robustness of the automated system in terms of its capacity to attend and absorb future innovation. Relatedly, there is a need for research in developing management processes and practices that are conducive to such continuous improvement. Overall, the areas of managing automation, human-robot interaction, and openness to innovation are potentially sources of competitive advantage beyond a particular technological solution.

Means (technologies)

At the core of our basic models lies the 'toolbox' of technologies and skills provided by numerous research fields, such as bioengineering, chemical engineering, electrical engineering, mechanical engineering, management engineering, computer sciences etc. For the cross-disciplinary research profile to succeed in achieving its set objectives, interlinkages, and interdependencies between the means must be unfolded (see use cases below for examples on how to connect the dots).



Exemplifying fictitious cases that connect the means

Case 1: Fictitious R&D case
An industrial biotechnology company relies on engineered microbes and fermentation to produce their products. As framework conditions are continuously and rapidly changing and markets are fluctuating, there is enormous pressure to dramatically reduce the time-to-market of novel products and furthermore diversify their product portfolio to be able to tackle new opportunities and become more resilient against ever-changing conditions.

To significantly reduce time-to-market and achieve a diversification of products, the company will have to reduce the time it takes to develop a new microbial production strain that is ready for scale-up. Strain development is currently slow and error prone due to the limited understanding of the relevant biology leading to high failure rates and often to tinkering with the biological unknown rather than straight-forward engineering. Furthermore, throughput is low as most experimental work is conducted by people manually. Lastly, new projects at the company tend to be started from scratch every time a new product is pursued, with limited learning from previous product development cycles.

In that context, the basic model suggests the application of the following principles and tools:

1. Closed-loop optimization based on data-driven Black box, White box and Hybrid modelling provides an avenue for algorithmically selecting the right genetic targets to engineer for improved production by efficiently navigating the biological unknown. Very fast Design-Built-Test-Learn (DBTL) cycles are needed for this to succeed (see figure 3).

2. … requiring a high degree of Laboratory Automation to bring down DBTL cycle times by both reducing manual labour and manual errors. Automated liquid handling, Microfluidics, Autonomous robots, Collaborative robots, Computer Vision and Augmented/Virtual Reality can all play a role here and developed solutions will have to be flexible and affordable enough to. Laboratory Automation will furthermore simplify …

3. … Data engineering, as data capture (presently conducted manually) can be fully automated based on Robotic Process Automation (RPA) and Software bots reducing DBTL cycle times even further and leading to more clean and complete data needed for step (1) to succeed.

Case 2: Fictitious manufacturing case
A pharma company is eager to drop batch production in favour of continuous manufacturing (to save costs), but numerous challenges put forward by GMP requirements make this transition difficult: (i) sterility can presently only be asserted through cultivations (~days) that make batch manufacturing a necessity to comply with GMP requirements and (ii) QC/QA needs to fundamentally be rethought to facilitate real-time monitoring of continuous production processes.

Working towards making continuous manufacturing a reality, the challenges i-ii can be addressed in the context of the basic model:

- Develop Autonomous robots (that can be sterilized) to replace human operators on the production lines and thus eliminate/reduce contaminations …

- … and develop advanced Sensor/Internet of Things (IoT) technologies that facilitate real-time Quality Assurance/Quality Control and control of operations based on approvable/explainable AI …

- … and that will also facilitate automated GMP documentation to replace Master Batch Records and thus reduce costs.

Case 3: Fictitious case that integrates R&D and manufacturing
Climate change has motivated the pursuit of artificial milk, meat, and fish alternatives that often rely on bioprocesses for production. Unfortunately, scaling bio-based products from bench to full-scale production (at the relevant volumes) is a very hard problem due to a high failure rate and limited understanding of how process conditions affect productivity at scale. Furthermore, development of novel products in R&D rarely considers the constraints and limitations put forward by the manufacturing side.

To help solve this issue, the following principles and means from the basic model should be applied:

- Adoption of a Systems Engineering approach to facilitate a holistic overview of the whole value chain by mapping out all processes and unit operations …

- … and modelling production capabilities (biological and mechanical) to be used in the R&D process to ensure R&D can incorporate manufacturing considerations early in the R&D process. Implement the capability models in IT tools (databases, simulation systems, configurators, expert systems etc.)

- … and adoption of a Product and Production Architecture to take out the guess work in R&D by imposing manufacturing constraints on product discovery and development and implementing standard biological parts and interfaces that facilitate diversification of product portfolios and facilitate the modelling and alignment of production architecture across production lines, laboratory facilities and IT infrastructures.

- Furthermore, the development of a Digital Twin of the whole value chain will enable collaboration across the whole organization, aid Systems Engineering and Product(ion) Architecture, and facilitate Advanced Process Control

- Together, these approaches will facilitate product development with “the End in mind” and thus reduce time-to-market and reduce failures during scale-up.

21st Bio

Feeding the world through automated fermentation

To Danish-American biotech start-up 21st. Bio, life science automation is about much more than optimizing profit.

"Life science automation is the key to our survival as a company and will ultimately be the answer to the challenge of feeding the global population," says CSO Per Falholt.

The company name has a dual meaning. Much like astronomers used to debate whether Pluto should count as a planet or not, there is an ongoing argument in the biotech community on the possible classification of selenocysteine as the 21st proteinogenic amino acid. Also, the name refers to one of the main challenges of the 21st century: how to feed the growing global population in a sustainable manner.

"Let's face it. There is no hope of us being able to reduce the carbon footprint of protein production in farm animals to an acceptable level. This form of production has been optimized through more than one thousand years, and it will just not be possible to optimize further to feed the growing population in this way without dramatic consequences for the climate. To my mind, there is only solution: recent biotech developments enable us to produce any given protein through fermentation at reasonably competitive cost," explains Per Falholt.

With active research groups and labs in Copenhagen and USA, 21st.Bio works with clients on establishing biotech manufacturing of various proteins intended for human consumption. While the details cannot be disclosed at this point due to client confidentiality, Per Falholt can give a broad outline:

"We are talking about proteins which are currently produced in farm animal systems at huge bulk quantities. On the one hand side, this equals a large market opportunity for our products, but on the other hand it is obvious that we need to be extremely focused on cost minimization, since these markets are very sensitive to even minor fluctuations in price."

Hence the focus on automation, he continues:

"While we do have ample opportunities for optimizing our current set-ups, this will not bring about the revolution we need to be truly competitive against conventionally produced proteins. Instead, we must take manufacture of fermented products to a new level through new equipment with a high degree of automation and digitization. Notably, these should be integrated allowing for automated collection of production data, analysis, and adjustments. In this manner, we will be able to save months relative to current production and R&D cycles."

"Fortunately, the timing is perfect as the various technologies we need have reached a high degree of maturity. By implementing them we will be able to learn much faster, and ultimately be able to reduce the price of our end products to competitive levels."

Still, mature technology is not enough, Per Falholt emphasizes:

"Chemical engineering candidates with both biochemical and automation qualifications are in very high demand. We already have open positions, and demand will certainly continue to rise."

ReShape Biotech

Let the robot do the (cultivation) dishes

Countless hours are spent by life science industry employees preparing cell-culture dishes. Danish startup Reshape Biotech produces a robot capable of preparing such plates, freeing up time for the skilled laboratory technicians to perform other tasks that create more value. Also, the company has a line of robots for trials monitoring. Both robot types have a characteristic common feature: they are small and simple.

"Many robot systems on the market are large, complex, and high-tech. They often end up not getting used. Instead, developing robots which are cheap and easy to operate has been our philosophy from the outset," says CEO Carl-Emil Grøn.

Within just three years, Reshape Biotech has grown to 17 employees and attracted millions of USD in venture capital. Customers are mainly biotech companies.

"We believe our solutions to be equally relevant for the pharma industry. However, since pharma is subject to many types of regulation and have very strict specifications, this is just a very expensive market to address. Therefore, our strategy is not to pursue this market for the time being," says Carl-Emil Grøn.

As an example, the CEO points to the size and shape of the most common cell-culture dish. The Petri dish was invented by German bacteriologist Julius Richard Petri in 1887.

"When Petri introduced his dish, it was giant leap forward. However, if invented today we would have chosen a much smaller size and more importantly, we would never have preferred a round shape – this is just not practical when you want to automize your processes," Carl-Emil Grøn comments, continuing:

"Basically, we are still in a phase of trying to develop robots which fit into industry manufacturing systems. At some point in time, we will have to make swap in mindset. We need to build manufacturing systems which are fit for robots!"

A handful of Reshape Biotech staffers have studied at DTU, Carl-Emil Grøn being one of them:

"I did my Bachelor at DTU. But at that point we were ready to start Reshape, and since I couldn't compose the content of my Master studies in a way relevant for the company, I decided to drop out and concentrate on being CEO."

What then would be his advice to DTU?

"I would ease up the current educational structure, allowing for more combinations. In my mind, it would be especially beneficial if the mechanics, electronics, and software disciplines could be integrated better into the life science sphere."

Notably, this integration would not only allow for better candidates leaving DTU, Carl-Emil Grøn underscores:

"The research at DTU would be first in line to benefit. I am certain that any life science research department will at minimum be twice as effective by hiring, say, three software engineers per research group to assist the life science researchers."

Further, the Reshape Biotech CEO has noted with interest a suggestion from Novo Nordisk and other stakeholders for a life science automation centre:

"We would surely be keen to employ candidates coming from such a centre. Currently we find it extremely difficult to recruit the people we need. We must either hire biotech people and train them extensively in software or vice versa. It would be a huge plus if candidates with a dual background were available."

SSI

How COVID triggered accelerated automation at SSI

Over very short time SSI (Statens Serum Institut), the national entity responsible for preparedness against infectious diseases in Denmark, had to scale-up its capacity for testing and analysis as the COVID-19 pandemic hit in spring 2020. This resulted in establishment of TestCenter Danmark at SSI.

"While the challenge was obviously huge, fortunately we didn't have to start from scratch in the IT automation domain. We had already implemented the highly automated digital infrastructure when we created the Danish National Biobank a few years earlier," says Bartlomiej (Bart) Wilkowski, head of systems development and data integration IT section at both the biobank and the test centre.

The Danish National Biobank contains more than 14 million biological samples such as serum, plasma, DNA etc. With the relevant permissions, scientists can access data for research purposes. Data storage and management of the biobank data flow are large and complex tasks. Still, the extensive COVID testing campaign was a significant additional challenge:

"Since we had a very high level of production, we were not able to optimize in the way we normally would. Especially during the most critical phase we had to be careful not to introduce new features," says Bart Wilkowski, continuing:

"Now, as things have calmed down, we are still operating the test system, but we are able to fine-tune procedures and introduce several exciting new features. Thus, should another COVID wave come, we will be well prepared."

For instance, SSI has implemented an integration of a robot able to react to positive test results, picking out the relevant samples for further testing.

"Basically, the more you can automate the better. However, some elements are trickier than others since you may need to modify the basic structure of your data to succeed. This is not always straightforward, and again not something you want to do while you are running at full speed."

An extra challenge during the pandemic was the emergence of new dominant variants along the way.

"For each new variant of concern, there is always a need to make several adjustments both in the labs and in the underlying data flow. We gradually improved our ability to adapt to new variants quickly. For instance, when the omicron variant came, we managed to make the transition in just two weeks. Still, we want to be able to react even faster. This is an ongoing focus."

Bart Wilkowski did his PhD at DTU.

"That was an exciting time for me. I was really impressed by the state of technological development at DTU. To my mind, the university is well positioned to produce the candidates needed for advancing life science automation further. Notably, it would be beneficial if some of the candidates would have cross-disciplinary skills allowing them to bridge data science with life science."

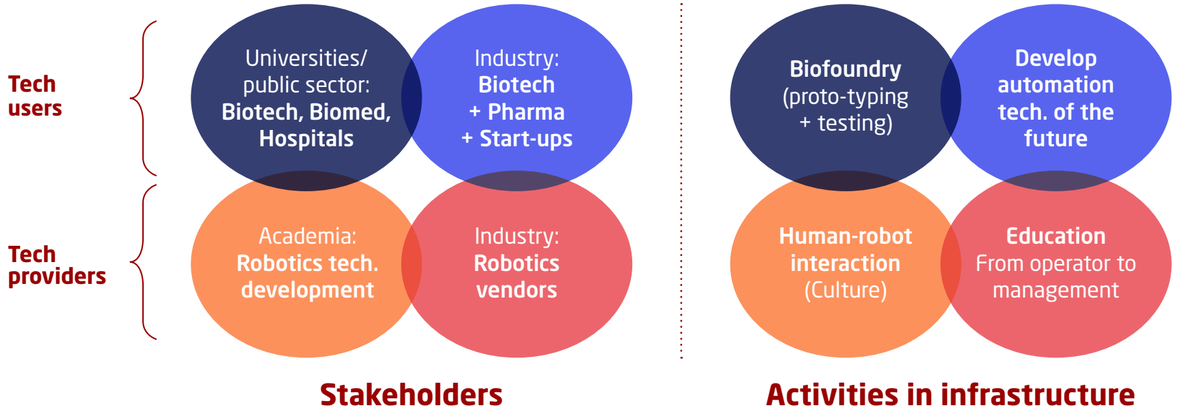
"Also, I would like to stress the importance of engineering students getting hands-on experience. I strongly advocate collaborations with both industry and institutions like SSI which have labs and are engaged in automation."

The research infrastructure

To achieve the objectives described in section 3, we propose a physical research infrastructure (Figure 7). In this, experts from both academia and industry and across all relevant scientific domains can jointly develop solutions using the described means and principles (see Figure 8 for a graphical illustration of a basic concept for a research infrastructure). The research infrastructure will furthermore facilitate the research-based teaching environment needed to establish a cross-disciplinary education that fosters the development of graduates with T-shaped skills, who have deep knowledge and skills in a particular area (e.g. molecular biology, management engineering, data science etc.) paired with the ability and wish to make connections across many different disciplines.

The infrastructure would further allow for the establishment of a knowledge hub, where the private and public sectors can interact and co-create the needed technological solutions, within robotics, automation, molecular biology, data structure and

Figure 7
Suggestion for a research infrastructure where the stakeholders can drive the technical development and education of the future experts within the life science automation area.



analysis. The infrastructure would further act as a biology proto-typing facility (Biofoundry) offering all DK researchers access to high-end automation solutions for the automated construction of genetically modified cells and characterization/ screening for functionality. An activity that will also act as a test-bed for the newly developed robotics solutions, and from which user-driven design will be fuelled.

Collectively, the hub would provide the means to reach the critical mass of cross-disciplinary expertise and thereby create the foundation for educating the future Life-Science engineers and providing continued education of the existing workforce, in state-of-the-art laboratories facilities.

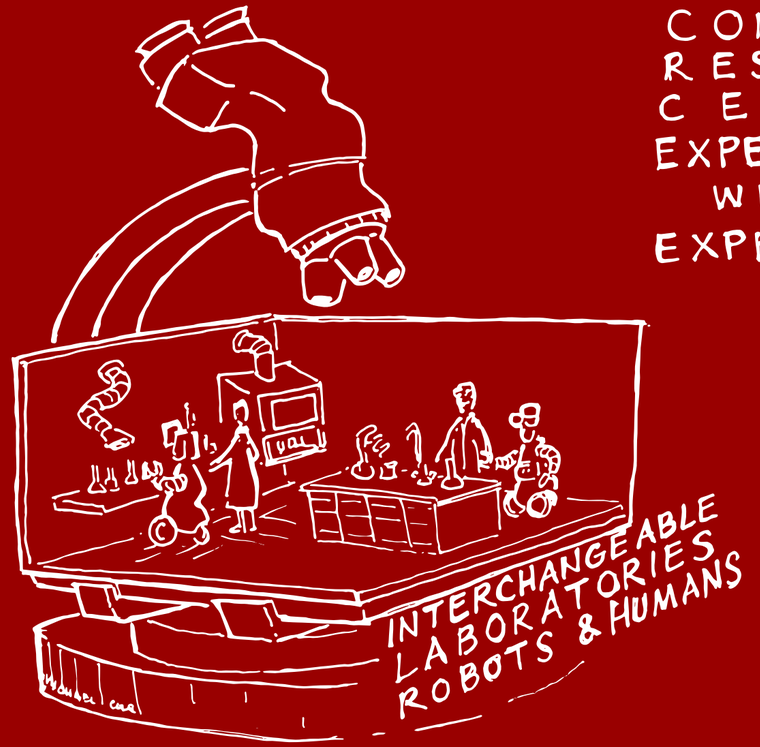


Figure 8
A graphical illustration of a basic concept for an Automation for the life science sector research infrastructure.

Recommendations for research and a roadmap for education, research infrastructure, and framework conditions

Automation within the life science sector requires considerable research effort. Some research efforts are dependent on other research efforts to have been conducted or initiated. Thus, a roadmap that outlines both the recommendations for research and the sequence of the different research efforts is key (it is important to stress that many research efforts will overlap, though).

Therefore, together with relevant private companies, public institutions, and trade organizations in Denmark, DTU aims to develop a roadmap for the development over the next 5-10 years which describes – step by step – the combinations of challenges, technologies, and framework conditions (if any).

The following is a tentative suggestion for recommendations for research and a roadmap.

Firstly, research must be conducted into modelling of the pipeline from R&D to manufacturing (from cell to reaction). How can this pipeline be broken down into modules (process architecture)? Which information is relevant to collect for digital twin solutions to be created?

Secondly, a clear understanding of the current and future workflows across the whole R&D and manufacturing value chain must be produced by modelling production capabilities including biological, chemical processes and the mechanical design of production and lab equipment. Research must be conducted into this and in this context, modularization and IT models of production capabilities to be used in R&D ought to be investigated.

Thirdly, research must be conducted into how to best develop sensor technologies and algorithms to enable data acquisition, structure data, ensure data quality, and set up a digital infrastructure. Including the development of common standards for data collection/formats across R&D, CMC, manufacturing and QA, both within and across companies. Research must be conducted into how automation can facilitate data capture and engineering and AI-based decision-making. This will guide equipment vendors to follow these guidelines (standards) and help eliminate redundant development efforts in multiple companies. Furthermore, research should be conducted on how AI and automation can be combined to replace both researchers' cognitive tasks and experimental workflows in life science R&D to make 'the robot scientist' mainstream and accelerate product discovery and hypothesis-driven research.

Fourthly, as automation within the life science sector is highly dependent on cross-disciplinarity – or expressed alternatively on the use of a multitude of technologies in combination – research must be conducted into system integration of the technologies. Here, research into system engineering, process analysis, product and production architecture, and digital twins of the R&D and manufacturing value chain for the life science space is of obvious relevance.

As a *fifth* area, research must be conducted into novel robotics solutions. These need to be affordable, easy to programme, safe and reliable, autonomous, and sufficiently flexible to provide real value in early-stage R&D. Moreover, they should fulfil standards for programming of robotics/automated systems and for connectivity between hardware and software. Documentation for soft- and hardware needs to be deployed in highly regulated manufacturing environments to facilitate continuous manufacturing. Also, such solutions must be aseptic and thereby acceptable for use in pharma-manufacturing settings. In this context, surface materials, lubricants, and robustness for sterilization should be investigated.

As a *sixth* effort, research must be conducted into how a balance can be struck between concerns for continuous manufacturing and other hand batch-based biological production, as well as craft-based R&D processes.

As a *seventh* effort, research should be conducted on how to reduce feedback time for QA by developing faster biological analysis process, design laboratory equipment and IT/ automation that allows for test of small batches in a short time.

As an *eight* area, research must be conducted into how private companies in the life science sector can organize human-centred design processes and into how ergonomics and Human Factors can help generate ownership and understanding in the workforce in the R&D lab and at the factory floor, while also improving the effectiveness of the R&D and manufacturing processes. Also, research should be conducted into how the human-robot collaboration is governed and into the opportunities for continuous system improvement and openness to radical innovation. Lastly, research must be conducted into, how such automation changes management practices in the interest of wellbeing, efficiency, and competitiveness?

Emerging automation technologies for the life science sector

Computational modelling

The main scope of computational modelling is to allow virtual design and validation of manufacturing processes. Further, in-line process monitoring via process analytical technologies (PAT) may generate the data needed to validate these models and secure regulatory approval. In the USA, the Federal Drug Administration (FDA) has published a draft guidance in which it proposes replacing 'three-batch validation' with a three-stage methodology that involves designing a suitable process, using the knowledge gained in development and scale-up; ensuring the process is capable of reproducibly manufacturing commercial batches; and validating it continuously during routine production. The conventional process of scaling up will also be replaced by 'numbering up' – i.e., using microreactors in parallel arrays. Numbering up has several significant advantages over traditional techniques. It dispenses with the need for costly and time-consuming studies to devise a process for scaling up chemical reactions, since the process that was used to produce a few grams of product in the laboratory is the same one that is used to synthesize larger quantities. In addition, using microreactors makes it much easier to control key parameters and thus improve yields.

Continuous processing and automation

Virtual engineering can facilitate reconfiguration of existing manufacturing lines. Combining flexible processes with miniaturized, modular components may facilitate fast modifications to the order in which operations are performed. Such improvements will allow pharma companies to create different supply chains for different product types and markets, manage sudden shifts in demand such as the step changes associated with live licensing and reduce their manufacturing costs. They should simultaneously help the industry fulfil its social responsibilities, including the need both to pioneer more sustainable manufacturing processes and to produce medicines the entire world can afford. By 2020, most medicines will also be manufactured continuously. Process tomography and other such technologies will enable companies to capture real-time data on critical processes, develop complex multivariate models and automatically compensate for unexpected process disturbances. Process data generated during the development phase will be used to 'teach' process control systems to respond to process disturbances even before commercial manufacturing begins. Meanwhile, advances in colloidal and foam systems will facilitate the micro-processing of active pharmaceutical ingredients (APIs).

Recommendations for education

University-level education in life sciences should include teaching automation and digitalization to foster the skill and mindset needed for the automation of life science R&D and production

Graduates possessing skills from both the biological and automation/digitalization domains are scarce, limiting the sector's efforts toward automated R&D and manufacturing. Thus, universities should aim to educate more candidates with cross-disciplinary knowledge.

- The solution would be to develop the existing educational programmes to introduce and exemplify the use of robotics/automation and analysis of big datasets in life science in relevant courses at BSc, MSc and PhD level for both the life science and classical engineering educations.
- A MSc/PhD level course in automated biology teaching the theoretical foundation for programming of robotics equipment, design of high-throughput experiments, design of automated production set-ups, and the analysis of large biological dataset from these
- To establish a teaching laboratory facility with robotics equipment and experimental courses where students can gain hands-on experience
- Fourthly, to establish an interdisciplinary project-based course where students from the life science, mechanical, electrical, and computation engineering educations can collaborate on joint projects, thereby fostering cross discipline communication skills

Continued education to upgrade the existing workforce's competencies will be essential for the successful transition to automation and digitalization of the life science sector

The scientists and technical staff in R&D, QA/QC, and manufacturing will need new technical competences. This relates both to the operation of the new automated equipment and for the analysis of the resulting larger datasets. The solution would be continued education courses targeting the different organizational levels of private companies:

- The technical/operator staff will need hands-on experience with programming, operating and maintaining robotic equipment.
- Scientists in R&D and QA/QC will need to learn how to design automated experiments and quality assurance programmes, and how to effectively handle the resulting data.
- Scientists in manufacturing will need to learn how to design automation of production line control, and how best to use the information for decision-making.
- Managers will need higher-level understanding of the advantages, limits, and pitfalls of implementing automation/digitalization.

The educational initiative should include all levels of the educational landscape to support the development of a common language and framework for life science automation

The introduction of automation in life science R&D, QA, and manufacturing requires that future technical staff can programme, service and operate such equipment. The current educational programmes for laboratory technicians, bio-analysts, and industrial operators do not include these elements.

The Universities should collaborate with relevant public educational institutions and private educational providers to establish a focused educational programme where students from these educations gains hands-on experience with programming, operating, and servicing automatic/ robotics equipment. A further advantage of such a cross-institutional effort will be the opportunity to establish common terminology and a language across all education levels. This will offer Denmark a competitive advantage over other countries and help build the new culture needed for successful automation.

Recommendations for a requirement specification for a research infrastructure

To support the above recommendations for research and education, a research infrastructure is needed. The facility should encompass a hybrid of laboratories, teaching facilities, offices, and meeting spaces. Thereby the day-to-day interaction between representatives from industry, university staff and students working on joint projects will be supported. The ambition should be for the facility to become the central life science automation hub in Denmark.

The laboratories for experimental biology and the development of automated solutions should include large open spaced wet laboratories for GMO work and mock-up production to allow for flexibility in placement of automation equipment in new configurations. The laboratory should provide students, researchers and companies access to cutting edge robotics, laboratory automation and digitalization equipment and technologies. The space will allow for testing the performance and usability of newly developed automation solutions (hardware, software, and workflows) with the relevant life science workforce. In addition, the laboratory will allow for research in ergonomics, human-machine interfaces, and change management. The co-location of R&D and Manufacturing automation research and people will effectively remove the artificial divide of both worlds. The research activities will ensure that critical mass is reached for a fruitful research environment needed to support the recommended educational activates. In addition to the high-end automation equipment, the site should include dedicated teaching laboratories with enough basic robotics equipment used in R&D and manufacturing to support the recommended educational initiatives.

Recommendations for framework conditions

The sector development project has uncovered a strong need for research into the systems aspects of automation. However, the funding system typically supports individual technologies rather than systems integration. We recommend for this practice to be changed, so that funding of research into systems integration can also be supported.

Appendix A

Steering committee members, list of interviewees

Steering committee members

Department director Friedrich Wilhelm Köster,
DTU Aqua

Department director Bjarke Bak Christensen,
DTU Bioengineering

Department director Kim Dam-Johansen,
DTU Chemical Engineering

Department director Per B. Brockhoff,
DTU Compute

Department director Hans Nørgaard Hansen,
DTU Construct

Department director Malene Kirstine Holst,
DTU Engineering Technology

Department director
Jan Henrik Ardenkjær-Larsen,
DTU Health Technology

Department director Mette Wier,
DTU Management

Senior Vice President Marianne Thellersen,
DTU (chair)

List of interviewees

CSO Per Falholt,
21st.bio

Senior director Anders Lomholt,
ALK-Abelló

Senior Research Scientist, Process Automation
Kim Olsson,
Chr. Hansen A/S

Vice president Rasmus Just,
Coloplast A/S

Senior manager Morten Lahrmann,
Fujifilm Diosynth Biotechnologies

Professor Kasper Støy,
IT University of Copenhagen (ITU)

Policy manager/Research and innovation
Anders Hoff,
The Danish Association of the Pharmaceutical Industry (LIF)

Policy manager/Clinical trials and
pharmaceutical manufacturing
Jakob Bjerg Larsen,
The Danish Association of the Pharmaceutical Industry (LIF)

Vice President for Corporate Product Quality
Assurance Ulrik Tolderlund,
Lundbeck A/S

Advisor Brian Schebye, Novo Nordisk A/S
Strategy Specialist Henrik Hegelund Louw,
Novo Nordisk A/S

Vice President, Automation and Process
Optimization James Love,
Novo Nordisk A/S

Senior manager Rasmus Di Sisto Bukkehave,
Novo Nordisk A/S

Senior project manager Lise Nørby Agersted,
Novo Nordisk A/S

Senior project manager Julie Rank,
Novo Nordisk A/S

Director Process Informatics & Analytics
Mads Thaysen,
Novozymes A/S

Senior Director Prototyping, Analytics and
Data Management, R&D, Anders Viksø-Nielsen,
Novozymes A/S

COO Magnus Nyborg Madsen,
ReshapeBiotech

CEO Carl-Emil Grøn Christensen,
ReshapeBiotech

Principal Automation & Screening Scientist
Helle Christiansen,
Roche

Director of Production and Logistics
Kirsten Moesgaard,
Smart Practice

Head of Development and IT Arieh Cohen,
Statens Serum Institut (SSI)

IT Section Head Bartlomiej Wilkowski,
Statens Serum Institut (SSI)

Notes

1. *The Pharma 1000: Top Global Pharmaceutical Company Report - Nov 2021 (torreya.com)*

2. *PVS_Life_Science_analyse_DK_web.pdf (dkpto.dk)*

3. Erhvervsministeriet (2021): Life science-industriens økonomiske fodaftryk, p. 26.

4. Erhvervsministeriet (2021): Life science-industriens økonomiske fodaftryk, p. 61-62.

5. CMC = Chemistry, manufacturing and controls step that links R&D with full-scale manufacturing.

6. *https://doi.org/10.1038%2Fnature02236*

7. *https://www.cam.ac.uk/research/news/artificially-intelligent-robot-scientist-eve-could-boost-search-for-new-drugs*

8. Reference will be provided in due time.

9. *https://application.wiley-vch.de/books/sample/3527341587_c01.pdf*

10. *https://en.wikipedia.org/wiki/AutoAnalyzer*

11. *https://dx.doi.org/10.1038%2Fsj.bjp.0707373*

12. *https://doi.org/10.1016/j.jpharm.2021.120554*

13. LIF (2021): Lægemiddelindustriens nøgletal.

14. Erhvervsministeriet (2021): Life science-industriens økonomiske fodaftryk, p. 26.

15. LIF (2021): Lægemiddelindustriens nøgletal.

16. Erhvervsministeriet (2021): Life science-industriens økonomiske fodaftryk, p. 55.

17. Erhvervsministeriet (2021): Life science-industriens økonomiske fodaftryk, p. 61-62.

18. LIF (2021): Lægemiddelindustriens nøgletal.

19. Erhvervsministeriet (2021): Life science-industriens økonomiske fodaftryk, p. 31. Also, high-quality research in Life Science may play an important role here (see LIF (2016): Om højkvalitetsforskning og dens betydning for dansk lægemiddelindustri. IRIS Group).

20. Erhvervsministeriet (2021): Life science-industriens økonomiske fodaftryk, p. 32.

21. PhRMA (2017): Prescription Medicines: Costs in Context; LIF (2017): Udvikling, antal biologiske og biosimilære produkter mod leddegigt og Innovative lægemidler, som skaber værdi.

22. Chemistry, Manufacturing and Control Management

23. T-shaped: Persons that both possess deep domain specific knowledge (vertical line in T) and at the same time a broader understanding of the field (horizontal line in T).

24. The company name has been anonymized for reasons of confidentiality.