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An Industry 4.0 Perspective

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4 Digital Twins in Smart Manufacturing

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4 Digital Twins in Smart Manufacturing

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4.1 BACKGROUND AND CONCEPT OF DIGITAL TWIN

The Fourth Industrial Revolution, which is also termed Industry 4.0, has arrived in full swing, and it has been influencing and driving all industries, including the high-tech manufacturing industry. It is well known that cyber-physical integration is incumbent for establishing a reliable and highly efficient smart manufacturing (SM) system in Industry 4.0 (Tao et al., 2019). This integration can be achieved by effectively implementing digital twin technology and services (Qi et al., 2018). Digital twin is driving SM after its rapid growth through the evolutional development of new products, services, and technologies, which include smart sensors, artificial intelligence (AI), internet of things (IoT), big data, cloud computing, augmented reality/virtual reality (AR/VR) devices (Židek et al., 2020), modeling and simulation (Shao et al., 2019).

There have been different versions of definitions of digital twin by different individuals and organizations/companies based on the application method in which they utilized digital twins. However, it is also likely to cause misunderstanding due to the several definitions flowing around each technology. A few examples of famous companies' definition of the digital twin is shown in Table 4.1. "A digital twin is a virtual representation of an object or system that spans its lifecycle, is updated from real-time data, and uses simulation, machine learning, and reasoning to help decision making" [IBM]. It can also be defined as a synchronized instance of a digital model or template representing an entity throughout its lifecycle and is sufficient to meet the requirements of a particular use case that the digital twin is meant to address. According to FANUC, the largest maker of industrial robots, "A digital twin is the concept of creating a digital replica of the physical machines, production processes or shop floor layouts in order to generate a number of competitive advantages." Moreover, "a digital twin is an integrated multiphysics, multiscale, probabilistic simulation of an as-built vehicle or system that uses the best available physical models, sensor updates, fleet history, etc., to mirror the life of its corresponding flying twin" (Shafto et al., 2010).

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TABLE 4.1
The Definition of Digital Twin According to Seven Different Companies

Company	Definition
IBM	"A Digital twin is a virtual representation of an object or system that spans its lifecycle, is updated from real-time data, and uses simulation, machine learning, and reasoning to help decision making."
Siemens	"Based on the consistent data model across all aspects of the product life cycle, some of the actual operations are accurately and veritably simulated."
General Electric	"Through the virtual models of devices and products, the actual complexities of physical entities are simulated, and insights are projected into applications."
NASA	"The application of interdisciplinary modeling and simulation across the product lifecycle."
ANSYS	"Combined outstanding simulation capabilities with powerful data analysis capabilities, it is to help enterprises gain strategic insights."
PTC	"PLM process is extended into the next design cycle to create a closed-loop product design process and help achieve predictive maintenance of the product."
FANUC	"A digital twin is the concept of creating a digital replica of the physical machines, production processes or shop floor layouts in order to generate a number of competitive advantages."

The digital twin can predict virtually everything that will happen in the physical world, thus providing valuable insights for future forecasting and development. This also allows testing and a better understanding of the product in the early stage, thus minimizing downtime and reducing cost. Digital twin technology is the future of designing and manufacturing a product, process, or service.

The digital twin is being used in the development of robots (Girletti et al., 2020) and autonomous vehicles and their sensor suites to enable testing in traffic and environment simulations. The digital twin implementation has a huge part to play in the testing, development, and validation of autonomous vehicles. The digital twin is also helping the healthcare industry through data by analyzing different circumstances of individual patients for their performance and by comparing them to the population and finding patterns to see trends. The digital twin also helps regulate and monitor the energy generation and capacity, especially wind turbines that can utilize the digital twin to integrate energy data and analyze energy growth avenues.

Supercomputing is the driving force of discovery in every field, from scientific to industrial, allowing researchers to understand the behavior of the smallest particles and visit the furthest expanses of the universe to unlock the meaning of life with digital twins; it is giving industries superpowers to time travel, letting them explore an infinite number of futures and decipher the past through different lenses. With million-X higher performance powered by accelerated computing, data center scalability, and AI, supercomputing will unlock new opportunities for us all.

This chapter also reviews the recent development of digital twin technologies in SM with special emphasis on smart product design, smart biomanufacturing, and IoT for SM from the perspective of Industry 4.0. This research work is expected to provide an effective guideline and broader view to the manufacturers and industry players of the key applications of the digital twin in SM. Successful stories of the world's reputed companies for utilization of digital twin for SM have been added to motivate individuals and companies who are planning to adopt digital twin technology for implementation.

4.2 DIGITAL TWIN-DRIVEN SMART PRODUCT DESIGN

The innovations being done in almost every technology depends heavily on digital twins, which delivers virtual representation of real-world products, systems, and urban infrastructures. For example, the product design of an electric motor can benefit from its digital twin, which can unveil its physical form, and also analyze its mechanical (rotation of the shaft, thermal conductivity) as well as electrical functions (current, voltage, sensors data). The digital twin greatly influences development, production, and operation by evolving through data flow, feedback via user experience, and incoming new data. A product's behavior can be simulated and analyzed well before its physical replica has been manufactured during product development. Three-dimensional printing for product design also relies almost entirely on digital twins. In a recent study performed by Siemens for the mixing of gases in micro-mixers, insights from the simulation of form and flow behavior were combined with generative algorithms. This helped Siemens to develop a unique micro-channel shape and configuration, which increased the mixing efficiency significantly. Digital twins can even help to simulate entire factories, including individual machines and their processes. As an example, let's consider the case of milling robots which experience large forces during the milling operation, leading to inaccurate movements. This problem can be solved by estimating these forces that push the robot away and compensating them in real time, keeping the robot in its path. With regards to operations, sudden disruptions caused due to sensor data of any real point in real-time can be compared to the simulation of that point and reliably predict the point parallel to operations using a digital twin. Digital twin opens new ways for development, production, and operations.

4.2.1 Case Study: Siemens

In the current car manufacturing industries, the development of cars is mostly done in a virtual environment. Siemens NX CAD is being used for successful product designing of vehicles. Automotive designers make their first model with clay to start with the design process, which is then converted into actual products through NX by automotive engineers. The digital twin of the car is created in the digital Enterprise solution portfolio. This enables the optimization of the product design before it's finally built.

Similarly, with the growth of the electric vehicle and energy storage industry, the demand for lithium-ion batteries is still proliferating, so battery manufacturers are focusing on optimizing and improving their processes to maintain the continuity of business in the market. Siemens provides proven automation and digitization solutions across multiple industries to help grow and sustain these businesses. Siemens digital twin technology facilitates manufacturing from automation and

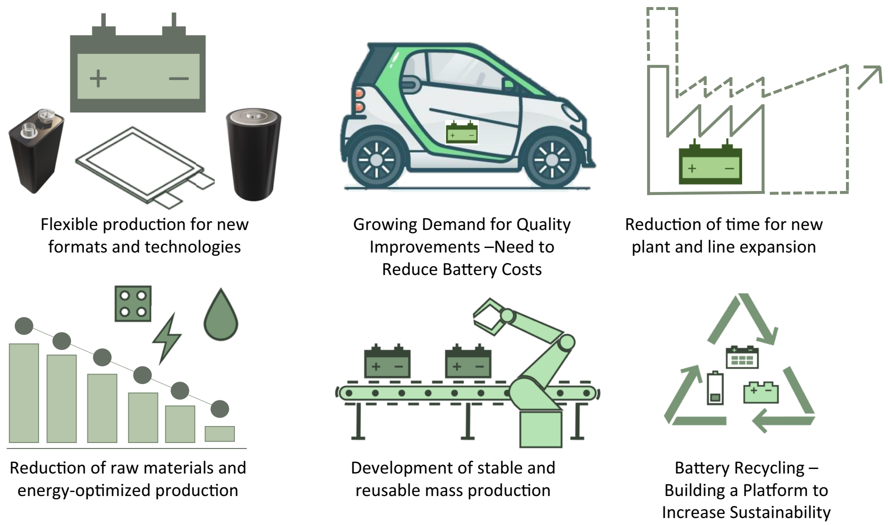

FIGURE 4.1 Battery production process (adapted from Siemens Korea Digital Industries (siemens.com Global website)).

drives technology to production planning and design software; Siemens can help to optimize every step of the battery manufacturing operation.

By establishing more flexible, transparent, and efficient processes in all areas of the cell, module, and pack production, one can ensure continued success in battery production and accelerate time to market, as shown in Figure 4.1.

4.2.1.1 Digital Twin in the Battery Industry

Siemens is the best partner to support industry-specific solutions for companies along the entire value chain, providing digital enterprise solutions optimized for battery manufacturing workflows using digital twins as described in its industry-specific solutions on (https://www.industry.siemens.co.kr/product/list.php?code=9&cat_flag=I).

Digital twins show an optimal virtual model of a product or production plant, intuitively show development throughout the entire lifecycle, and easily show operators to predict behavior, optimize performance, and gain insights from previous design and production experiences.

Siemens's comprehensive digital twin concept consists of three components, as shown in Figure 4.2: a digital twin of products, a digital twin of production, and a digital twin of performance of products/production. Siemens is the only company that can make an offer from a holistic point of view, as it provides sufficient industry-specific expertise and optimized tools.

4.2.1.2 Real-World Battery Performance Improvement Through Virtualization

A product's digital twin integrates all technology domain information into one data model. This allows simulation, testing, and battery performance optimization within the virtual environment to identify and correct possible problems or defects before

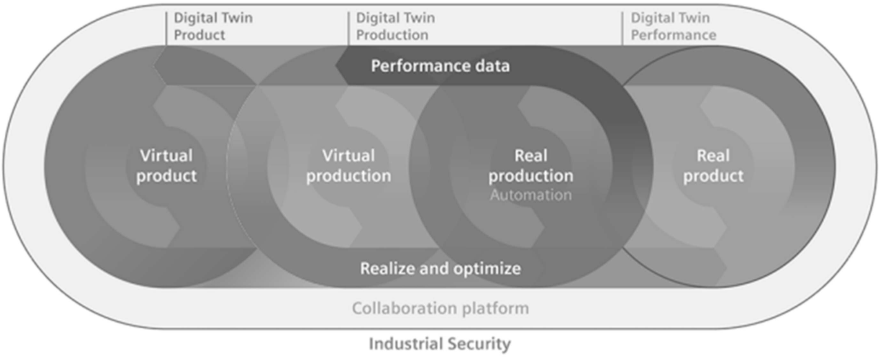

FIGURE 4.2 Components of Siemens' Digital twin concept (adapted from Siemens Korea Digital Industries (siemens.com Global website)).

actual battery mass production. These continuous data can be used as basic data in other fields of work, such as preliminary research, design, and instrumentation.

4.2.1.3 Optimization of the Entire Plant

As battery products are virtually designed and tested before production, production lines can also be planned, simulated, and optimized in a virtual environment with a digital twin implementation.

4.2.1.4 Data-Driven Optimization of Production and Product Performance

Currently, batteries and production processes generate vast amounts of data for product versatility and efficiency. Digital twins allow for continuous improvement by embracing and analyzing this production data in a virtual environment which gives enough data to make decisions in the real world.

In the battery production environment, these strengths enable operators to improve their products and create new business opportunities through accurate analysis of production data. Siemens' software cover the entire production process, from graphical modeling to virtual commissioning and line monitoring. Siemens utilized the digital twin to develop a world record-setting of an electric aircraft motor that not only weighs 50 kilograms but is also five times more powerful than comparable electric motors.

4.3 DIGITAL TWIN FOR SMART BIOMANUFACTURING

Due to the ineffective methods being adopted, developing a drug may cost a billion dollars and an average of ten years. Cell cultures in Petri dishes do not resemble organs or human diseases, and animal experiments are often unsuitable because animals are not human beings. Therefore, drug development is costly and takes much time. That is also true for toxicity tests for cosmetics, chemicals, and food products. Organ-on-a-chip (OOAC) technology has recently been introduced into the healthcare and personalized medicine industry to revolutionize biopharma research, development, and manufacturing (Van Den Berg et al., 2019). OOAC technology has the potential to use artificial intelligence and machine learning to reduce drug discovery times and costs and the potential to replace animal testing (Li et al., 2022) by incorporating bioreactors, and tissue culture (Tay et al., 2016) technologies. OOAC is a physical model of an organ or organs replicated on a device called a "chip." The chip involves growing tiny versions of organs from living cells in cavities and channels. In these devices, we can make three-dimensional cell cultures of human cells in an environment that closely mimics what is actually present in the human body. The living cells are provided nutrients and oxygen via cellular media and extracellular matrix circulated through microchannels. The whole system is known as the Microphysiological system (Wang et al., 2018; Ahadian et al., 2018; Wang et al., 2016; Skardal et al., 2016; Zhang et al., 2017), which consists of the OOAC device, pumping system (Chen et al., 2019; Yang et al., 2019; Li et al., 2019; Lohasz et al., 2019; Edington et al., 2018; Satoh et al., 2018), tubing, nutrients' reservoirs, oxygen cylinder, sensors, and process monitoring equipment (Zhang et al., 2018). Some researchers have tried to integrate multiple OOAC devices to form a micro-multiphysiological system termed as body-on-a-Chip (Sung et al., 2013) that replicates the dynamics of the whole-body response. Medicine/drugs can be tested on individual OOAC devices to understand the response of medicine to the cells, and the same phenomenon can be translated to have a closer look at the whole body's response to the introduction of a particular medicine. Through this technology, drug testing is being done for the most common diseases, i.e., diabetes, kidney (Pietilä et al., 2014; Jang et al., 2013), lung (Huh et al., 2012; Geraili et al., 2018; Baker et al., 2011; Huh et al., 2013), liver (Gröger et al., 2018; Lee et al., 2018), and cardiovascular (Ahn et al., 2018; Parker et al., 2019) diseases. Digital twins are digital replicas of an object, process (Silfvergren et al., 2021), or system (Sundqvist et al., 2022) – and in this case: a human patient. In the future, a digital copy of every human body – a digital twin – may be used to help humans live healthy life. To achieve this goal, behavioral scientists, psychologists, doctors, and software developers, are working together to develop mathematical models (Herrgårdh et al., 2021a, 2021b, Herrgårdh et al., 2022) as tools for better health (Sundqvist 2022). In recent studies, various biosensors have been implemented in the OOAC systems for online monitoring of vital parameters like pH (Mousavi et al., 2016), oxygen (Brennan et al., 2014), CO_2, Virtual reality (VR) (TEER) (Maoz et al., 2017; van der Helm et al., 2019), and various other biomarkers. A recent research work demonstrates the use of albumin immunosensors to monitor the microphysiological system of liver-on-a-chip (Asif et al., 2021), as shown in Figure 4.3. In another work, real-time monitoring of liver fibrosis was done in a microphysiological system via embedded sensors (Farooqi et al., 2021). The actual image of the liver fibrosis-on-chip and the components associated with it have been shown in Figure 4.4. The same group developed a microfluidic chip platform enclosure with a microfluidic chip connected to a micropump for media circulation and to an optical pH sensor for pH measurements (Ali et al., 2020). A portable fluorescence microscope is also installed right above the microfluidic organ chip for real-time visual monitoring. Other components include bubble remover, heater, fan, and control stages, as shown in Figure 4.5.

Using digital twins technology, the OOAC manufacturing industry can save a lot of time and resources by making digital twins of individual organs and

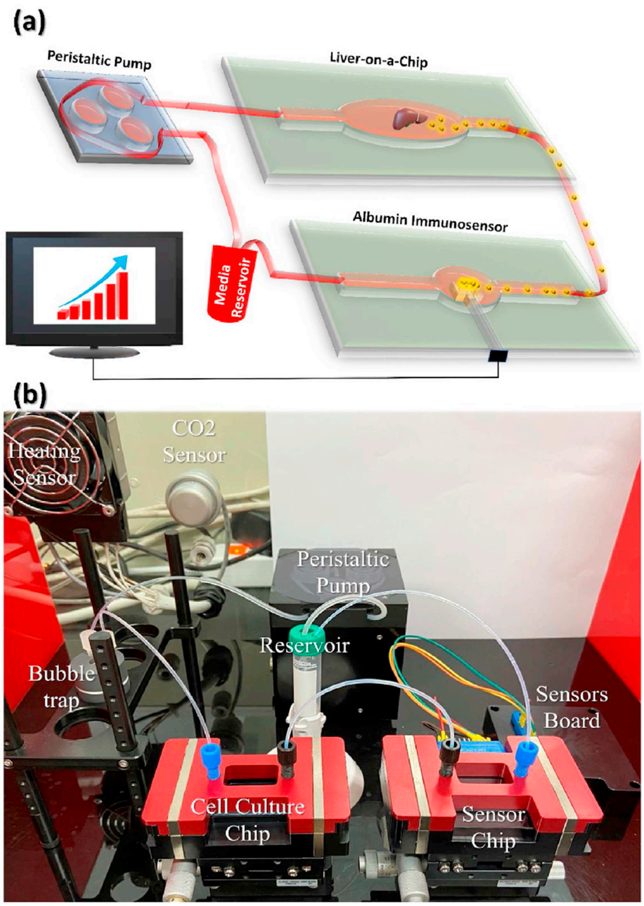

FIGURE 4.3 (a) Schematic of microphysiological system of liver-on-a-chip with albumin immunosensor; (b) actual image of the microphysiological system (adapted from Asif et al., 2021).

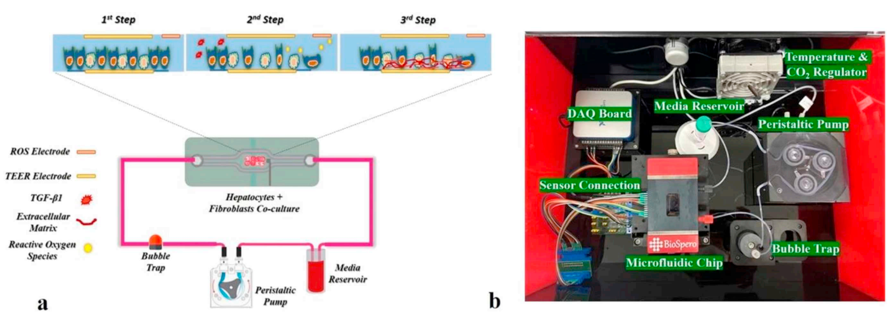

FIGURE 4.4 (a) The liver fibrosis-on-chip schematic; (b) The actual image of the liver fibrosis-on-chip device and associated components (adapted from Farooqi et al., 2021).

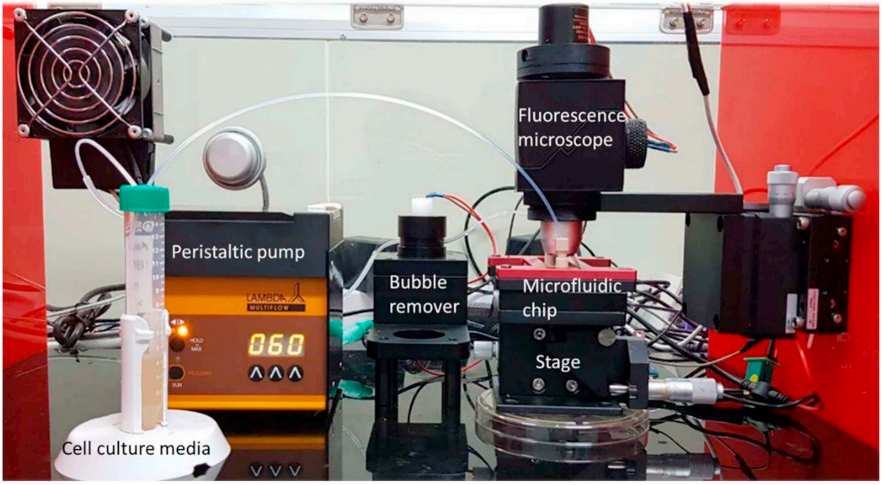

FIGURE 4.5 Actual platform image of the experimental setup for the online monitoring of ROS in breast cancer cell line MCF-7 (adapted from Ali et al., 2020).

multi-organ platforms. Microfluidic simulations of the tubing, pumps, reservoirs, and cavities can help in the SM of the physical structure of the OOAC platform. Cell growth-rate simulations, as well as soft sensors for monitoring vital parameters, can help in the SM of the sensors and cell-culture layers within the channels and cavities.

Biomicrofluidic researchers at the Delft University of Technology have proposed a flow control microfluidic device for next-generation OOAC experiments, as shown in Figure 4.6 (Özkayar et al., 2022). This configuration is suitable for kidney-on-a-chip

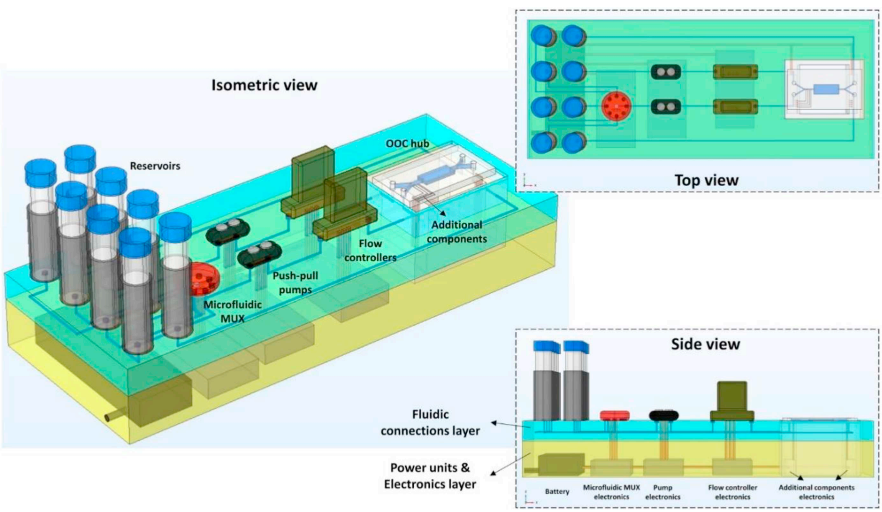

FIGURE 4.6 A microfluidic platform architecture of push-pull mechanism designed for double channel and double chamber OOAC device (adapted from Özkayar et al., 2022).

and uses a modular configuration of a push-pull mechanism. In addition, the flow of fluids from different reservoirs is controlled by the microfluidic multiplexer added to the second channel. Two layers of fluidic and electronics are connected to the microfluidic components via interconnections. The OOAC hub window is used for inverse and upright microscopy. The desired configurations can be achieved when needed by permitting the exchange of fluidic components in the top layer (out of plane).

4.4 DIGITAL TWINS AND THE INTERNET OF THINGS FOR SM

Digital twin for IoT is the way of virtually representing the elements and the dynamics of IoT operation and its working throughout its lifecycle. The ways in which the design, build, and operations of an IoT device are constructed are heavily influenced by the digital twin. In the design phase, different aspects of engineering work together synergistically to collaborate into a single facility of operational-oriented design. Particularly, the physical components, along with the physical bill of materials (BOM), collaborate with the virtual components such as software, sensors, chips, etc. This collaboration brings out the highest quality product by virtue of the digital twin. In the build phase, the digital twin helps in better understanding the influence of the product's tolerances on the devices that make the product. Moreover, its also about the improvement of the manufacturing process through the correction of tolerances and outcomes that are desired in the product.

Lastly, the actual operation of the product is facilitated by the digital twin. During the product's life cycle, the products are significantly influenced by their environmental changes, and they go through various physical and virtual changes over time, so the digital twins need to adjust to those changes with the products as they age. This feedback through the digital twin helps facilitate operations. It also helps to improve the design and manufacturing through the lessons that are learned and the recalibration that takes place along the way.

4.4.1 Case Study: Covestro

As project manager of Covestro's digital ChemLab, Lennart oversees supporting R&D labs with digital methods and new technologies. He aims to boost R&D innovative potential by allowing researchers to collect more results and insights more quickly from fewer experiments. Ultimately this approach is expected to shorten product development timelines.

To make a significant impact, Lennart knew that he had to focus on reducing the time researchers spend on data collection while simultaneously increasing data quality at the point of experimentation. He decided to leverage recent advances in speech recognition technologies to enable hands-free documentation at the bench.

LabTwin (https://www.labtwin.com/) offers the opportunity to tackle several challenges with a single digital solution. By providing hands-free documentation to lab workers, LabTwin enabled both an increase in the quantity of data recorded without slowing down experiments and a decrease in the risk of contamination by avoiding the need to go back and forth between lab benches and offices. By offering researchers a method of contemporaneous data capture and data access, LabTwin could also reduce the number of manual data entry errors and prevent data loss, thus improving data quality. Finally, as the collected data is automatically digitized, scientists no longer need to retype their notes at the end of each experiment, saving significant time and ensuring original data records are truly contemporaneous.

As a first step, Covestro decided to roll out LabTwin for two very different use cases leveraging the various capabilities of the digital lab assistant. The first use case was to guide the preparation of polymer mixtures with the IoT integration. The second use case was to support documentation of time-sensitive foaming processes with hands-free data capture.

4.4.1.1 Use Case 1: Polymer Formulation

Scientists prepare the polymer foam mixture by following a recipe that lists the different components to be weighed and mixed.

4.4.1.1.1 Challenges

Data Quality and Integrity: A tolerance margin allows the actual reagent weight to differ from the recipe weight. These variations need to be recorded as they can significantly impact the result.

4.4.1.1.2 Contamination Risk

Using printed protocols for polymer recipes or going back and forth to the office from the lab to access data is a potential risk of contamination with hazardous chemicals.

4.4.1.1.3 LabTwin Solution

As a digital lab assistant, LabTwin can verbally guide Covestro scientists through formulation steps and streamline their documentation by harnessing IoT integration. Captured data is automatically structured and enriched with metadata, increasing data quality and integrity. In addition, Covestro scientists leverage this human-machine interaction to maintain the recipe ratio with integrated recalculations, saving time and reducing potential waste of components. Enabling digital data access and capture can strongly reduce the need for paper in the lab, and at the end of the day, data can be exported or systematically uploaded to the data repository, cutting down extra data processing. The workflow of Covestro's digitalization with LabTwin for polymer formulation is shown in Figure 4.7.

4.4.1.2 Use Case 2: Foam Characterization

Once the polymer reagents are mixed, the foam starts forming. Scientists must capture the different stages of foam formation, as this information will be used for product development. Researchers must also record observations and measurements from various characterization tests.

4.4.1.2.1 Challenges

Data Quality and Integrity: The foaming process is very fast; therefore, scientists must handle the experiment while mentally storing timings and observations,

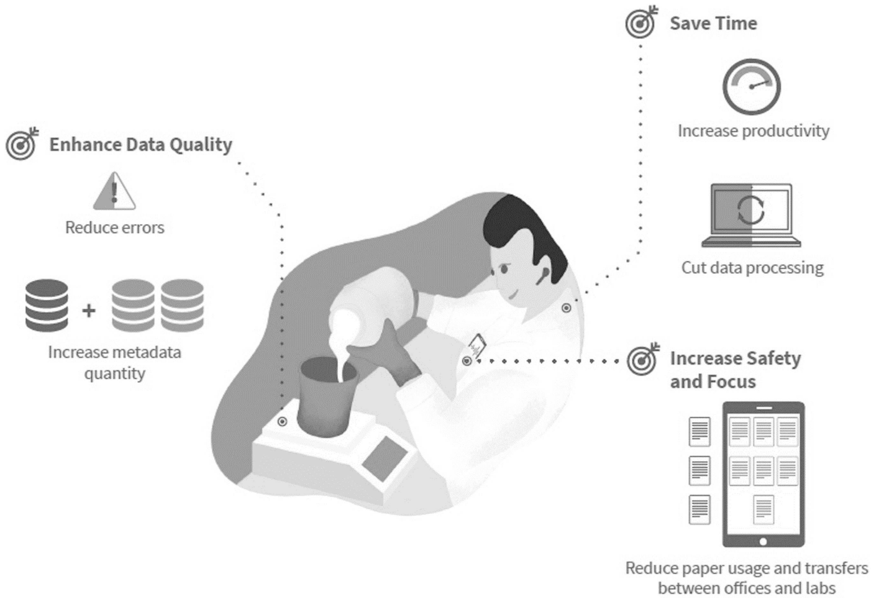

FIGURE 4.7 Covestro aims to increase R&D data quantity and quality, reduce paper as well as gain time using LabTwin's solution.

which would be written down later. Such multitasking increases the risk of errors and data loss.

4.4.1.2.2 Double Documentation

Scientists record their observations and measurements on paper at the point of experimentation and then type the data into computers after the experiment.

4.4.1.2.3 LabTwin Solution

With hands-free documentation, Covestro scientists can keep their eyes on the foaming process while voicing their observations, which LabTwin automatically digitizes and tags with timestamps. Researchers can easily augment the digital data with pictures.

Using LabTwin to support documentation of foaming workflow can significantly improve data quality and integrity. Covestro scientists capture more parameters with this feature, reduce the need to use paper in the lab, and will significantly decrease time wasted on retyping data. The workflow of how Covestro streamlines foaming documentation with LabTwin is shown in Figure 4.8.

4.4.2 Case Study: Digital Twin Solution in Machining Operation by FANUC

FANUC, a world leader in robotics and automation solutions, has developed technology for implementing digital twin technology in machining operations. This

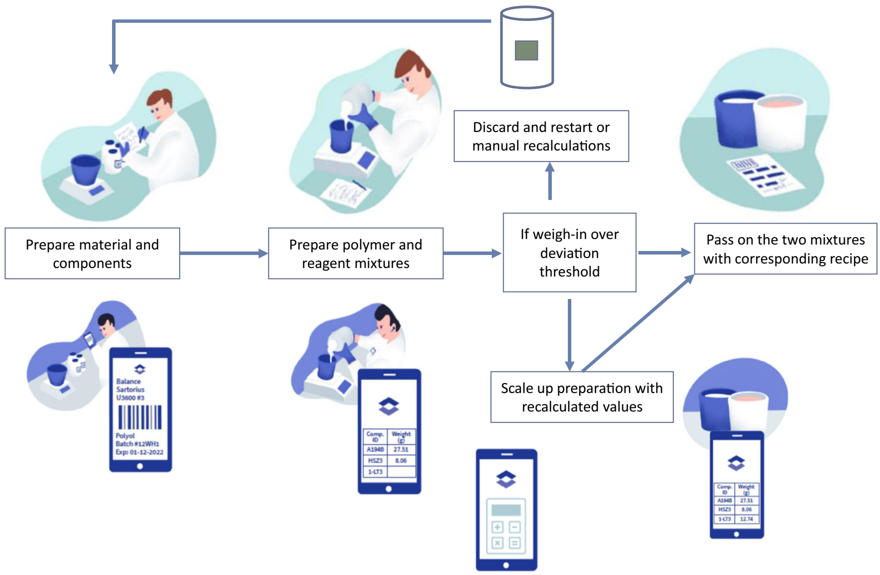

FIGURE 4.8 How Covestro digitalizes its polymer formulation workflow with LabTwin.

has been achieved using the newly released FANUC software, SURFACE ESTIMATION, on Victor Taichung's 5-axis machining center Vcenter-AX630. The objective of the application was to foresee the actual cutting texture on part surface by digital twin. The operation was affected by several factors such as (a) the mismatch between the tool paths generated by CAM and the actual cutting path; (b) unsatisfactory parameter settings of CNC control; (c) inefficient servo system response; and (d) thermal displacement, to name a few. The new software from FANUC has features to improve the shortcomings of the existing system. The software includes the machine servo parameters into the system to match the actual cutting operation. This gives the user the option to run the program on the real part only if the simulated result is satisfactory.

4.5 APPLICATION FRAMEWORK FOR PRODUCT/PROCESS DESIGN USING DIGITAL TWINS

4.5.1 Future Trends

The digital twin market was valued at USD 10.27 billion in 2021, and it is expected to reach a value of USD 61.45 billion by 2027, registering a CAGR of 34.48% over the forecast period, 2022–2027. The increase in adoption of 3D printing, sensors, and AI in the SM industries, i.e., product designing, healthcare, IoT, etc., is going to cause an increase in demand for digital twins technology and services. It is expected that simulation technologies for digital twins in smart manufacturing could grow at a rate of 7.1% to USD 2.6 billion by 2030 (*Global Digital Twin Market, By Type, By Technology, By Application, By End User, By Region, Competition, Forecast & Opportunities, 2017–2027F*).

4.5.2 Application Framework

If one has the capability to utilize digital twin technology, it certainly has enormous benefits for the manufacturer because it can provide value in multiple dimensions. It can improve the safety of operations because the digital twin manufacturer can first simulate a lot of scenarios, even before putting the physical product in, to make sure that the product actually works as it is designed. Even after the product is being used, the physical product is being manufactured and delivered to the customer, and they can constantly get real-time information, and a lot of times, can predict the process on certain days. Any deviation in the product performance can be predicted, and an early warning system can be developed, which can reduce uncertainty and help improve safety.

Considering the field of study, i.e., digital twin in SM in full development, more research studies are required to contribute. To have a broader view of the digital twin in SM, researchers and industrialists from different countries should discuss collaborations on international forums. One such event was organized by the University of Applied Sciences and Arts of Switzerland, i.e., CMS 2022 55th CIRP International Conference on Manufacturing Systems.

In smart biomanufacturing, Multi OOACs will be developed through digital twins, which relate to channels through which fluids can be pumped, and therefore medicines can be tested. Initially, only vital organ chips will be developed for the lung, liver, kidney, and heart. However, in the future, it will be possible to make these chips for all kinds of organs of the human body. This will be an important development in smart biomanufacturing because this standardized and modular approach is ideal for work-flows in the pharmaceutical, food, and cosmetics industries. It requires a dedicated and collaborative team consisting of technical people all the way up to biomedical researchers. There is also a great need for the support of industrial partners, from makers to applicators. The digital twin-enabled smart manufacturing of multi-OOAC will lead to better, cheaper, and more effective drug development, and this also applies

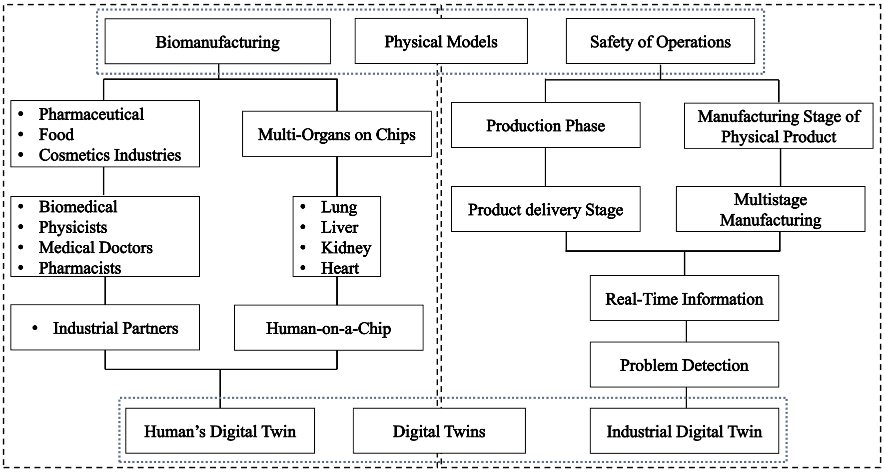

FIGURE 4.9 Overview of the application framework for Digital Twin for Smart Manufacturing.

to toxicity testing in the cosmetics and food industries. It is also expected to boost the world economy and open up a new market in OOAC. The overall application framework for digital twins in smart manufacturing is given in Figure 4.9.

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REFERENCES

Ahadian, S., Civitarese, R., Bannerman, D., Mohammadi, M. H., Lu, R., Wang, E., Davenport-Huyer, L., Lai, B., Zhang, B., Zhao, Y., Mandla, S. 2018. Organ-on-a-chip platforms: A convergence of advanced materials, cells, and microscale technologies. *Advanced Healthcare Materials*, 7(2): 1700506.

Ahn, S., Ardoña, H. A. M., Lind, J. U., Eweje, F., Kim, S. L., Gonzalez, G. M., Liu, Q., Zimmerman, J. F., Pyrgiotakis, G., Zhang, Z., Beltran-Huarac, J. 2018. Mussel-inspired 3D fiber scaffolds for heart-on-a-chip toxicity studies of engineered nanomaterials. *Analytical and Bioanalytical Chemistry*, 410(24): 6141–6154.

Ali, M., Kim, Y. S., Khalid, M. A. U., Soomro, A. M., Lee, J. W., Lim, J. H., Choi, K. H., Ho, L. S. 2020. On-chip real-time detection and quantification of reactive oxygen species in MCF-7 cells through an in-house built fluorescence microscope. *Microelectronic Engineering*, 233: 111432.

Asif, A., Park, S. H., Soomro, A. M., Khalid, M. A. U., Salih, A. R. C., Kang, B., Ahmed, F., Kim, K. H., Choi, K. H. 2021. Microphysiological system with continuous analysis of albumin for hepatotoxicity modeling and drug screening. *Journal of Industrial and Engineering Chemistry*, 98: 318–326.

Baker, M. 2011. Technology feature: A living system on a chip. *Nature*, 471(7340).

Brennan, M. D., Rexius-Hall, M. L., Elgass, L. J., Eddington, D. T. 2014. Oxygen control with microfluidics. *Lab on a Chip*, 14(22): 4305–4318.

Chen, Z., He, S., Zilberberg, J., Lee, W. 2019. Pumpless platform for high-throughput dynamic multicellular culture and chemosensitivity evaluation. *Lab on a Chip*, 19(2): 254–261.

Edington, C. D., Chen, W. L. K., Geishecker, E., Kassis, T., Soenksen, L. R., Bhushan, B. M., Freake, D., Kirschner, J., Maass, C., Tsamandouras, N., Valdez, J. 2018. Interconnected microphysiological systems for quantitative biology and pharmacology studies. *Scientific Reports*, 8(1): 1–18.

Farooqi, H. M. U., Kang, B., Khalid, M. A. U., Salih, A. R. C., Hyun, K., Park, S. H., Huh, D., Choi, K. H. 2021. Real-time monitoring of liver fibrosis through embedded sensors in a microphysiological system. *Nano Convergence*, 8(1): 1–12.

Geraili, A., Jafari, P., Hassani, M. S., Araghi, B. H., Mohammadi, M. H., Ghafari, A. M., Tamrin, S. H., Modarres, H. P., Kolahchi, A. R., Ahadian, S., Sanati-Nezhad, A. 2018. Controlling differentiation of stem cells for developing personalized organ-on-chip platforms. *Advanced Healthcare Materials*, 7(2): 1700426.

Girletti, L., Groshev, M., Guimarães, C., Bernardos, C. J., de la Oliva, A. 2020, December. An intelligent edge-based digital twin for robotics. In *2020 IEEE Globecom Workshops (GC Wkshps*, 1–6. IEEE.

Gröger, M., Dinger, J., Kiehntopf, M., Peters, F. T., Rauen, U., Mosig, A. S. 2018. Preservation of cell structure, metabolism, and biotransformation activity of liver-on-chip organ models by hypothermic storage. *Advanced Healthcare Materials*, 7(2): 1700616.

Herrgårdh, T., Madai, V. I., Kelleher, J. D., Magnusson, R., Gustafsson, M., Milani, L., Gennemark, P., Cedersund, G. 2021a. Hybrid modelling for stroke care: Review and suggestions of new approaches for risk assessment and simulation of scenarios. *NeuroImage: Clinical*, 31: 102694.

Herrgårdh, T., Li, H., Nyman, E., Cedersund, G. 2021b. An updated organ-based multi-level model for glucose homeostasis: Organ distributions, timing, and impact of blood flow. *Frontiers in Physiology*, 12: 619254.

Herrgårdh, T., Hunter, E., Tunedal, K., Örman, H., Amann, J., Navarro, F. A., Martinez-Costa, C., Kelleher, J. D., Cedersund, G. 2022. Digital twins and hybrid modelling for simulation of physiological variables and stroke risk. *bioRxiv*.

Huh, D., Leslie, D. C., Matthews, B. D., Fraser, J. P., Jurek, S., Hamilton, G. A., Thorneloe, K. S., McAlexander, M. A., Ingber, D. E. 2012. A human disease model of drug toxicity-induced pulmonary edema in a lung-on-a-chip microdevice. *Science Translational Medicine*, 4(159): 159ra147–159ra147.

Huh, D., Kim, H. J., Fraser, J. P., Shea, D. E., Khan, M., Bahinski, A., Hamilton, G. A., Ingber, D. E. 2013. Microfabrication of human organs-on-chips. *Nature Protocols*, 8(11): 2135–2157.

Jang, K. J., Mehr, A. P., Hamilton, G. A., McPartlin, L. A., Chung, S., Suh, K. Y., Ingber, D. E. 2013. Human kidney proximal tubule-on-a-chip for drug transport and nephrotoxicity assessment. *Integrative Biology*, 5(9): 1119–1129.

Lee, S. Y., Sung, J. H. 2018. Gut–liver on a chip toward an in vitro model of hepatic steatosis. *Biotechnology and Bioengineering*, 115(11): 2817–2827.

Li, J., Chen, J., Bai, H., Wang, H., Hao, S., Ding, Y., Peng, B., Zhang, J., Li, L., Huang, W. 2022. An overview of organs-on-chips based on deep learning. *Research*, 2022:20.

Li, Z., Seo, Y., Aydin, O., Elhebeary, M., Kamm, R. D., Kong, H., Saif, M. T. A. 2019. Biohybrid valveless pump-bot powered by engineered skeletal muscle. *Proceedings of the National Academy of Sciences*, 116(5): 1543–1548.

Lohasz, C., Frey, O., Bonanini, F., Renggli, K., Hierlemann, A. 2019. Tubing-free microfluidic microtissue culture system featuring gradual, in vivo-like substance exposure profiles. *Frontiers in Bioengineering and Biotechnology*, 7: 72.

Maoz, B. M., Herland, A., Henry, O. Y., Leineweber, W. D., Yadid, M., Doyle, J., Mannix, R., Kujala, V. J., FitzGerald, E. A., Parker, K. K., Ingber, D. E. 2017. Organs-on-chips with combined multi-electrode array and transepithelial electrical resistance measurement capabilities. *Lab on a Chip*, 17(13): 2294–2302.

Mousavi Shaegh, S. A., De Ferrari, F., Zhang, Y. S., Nabavinia, M., Binth Mohammad, N., Ryan, J., Pourmand, A., Laukaitis, E., Banan Sadeghian, R., Nadhman, A., Shin, S. R. 2016. A microfluidic optical platform for real-time monitoring of pH and oxygen in microfluidic bioreactors and organ-on-chip devices. *Biomicrofluidics*, 10(4): 044111.

Özkayar, G., Lötters, J. C., Tichem, M., Ghatkesar, M. K. 2022. Toward a modular, integrated, miniaturized, and portable microfluidic flow control architecture for organs-on-chips applications. *Biomicrofluidics*, 16(2): 021302.

Parker, K. K. 2019. Designer assays for your sick, subdivided heart. *Cell*, 176(4): 684–685.

Pietilä, I., Vainio, S. J. 2014. Kidney development: An overview. *Nephron Experimental Nephrology*, 126(2): 40–44.

Qi, Q., Tao, F. 2018. Digital twin and big data towards smart manufacturing and industry 4.0: 360 degree comparison. *IEEE Access*, 6: 3585–3593.

Satoh, T., Sugiura, S., Shin, K., Onuki-Nagasaki, R., Ishida, S., Kikuchi, K., Kakiki, M., Kanamori, T. 2018. A multi-throughput multi-organ-on-a-chip system on a plate formatted pneumatic pressure-driven medium circulation platform. *Lab on a Chip*, 18(1): 115–125.

Shao, G., Jain, S., Laroque, C., Lee, L. H., Lendermann, P., Rose, O. 2019 December. Digital twin for smart manufacturing: The simulation aspect. In *2019 Winter Simulation Conference (WSC)*, 2085–2098. IEEE.

Shafto, M. Conroy, M. Doyle, R. Glaessgen, E. Kemp, C. LeMoigne, J. Wang, L. 2010. *Draft modeling, simulation, information technology and processing roadmap*. National Aeronautics and Space Administration, https://www.nasa.gov/pdf/501321main_TA11-MSITP-DRAFT-Nov2010-A1.pdf (accessed on 7 June 2023).

Silfvergren, O., Simonsson, C., Ekstedt, M., Lundberg, P., Gennemark, P., Cedersund, G. 2021. Digital twin predicting diet response before and after long-term fasting. *PLOS Computational Biology,* 18(9):e1010469

Skardal, A., Shupe, T., Atala, A. 2016. Organoid-on-a-chip and body-on-a-chip systems for drug screening and disease modeling. *Drug Discovery Today*, 21(9): 1399–1411.

Sundqvist, N., Grankvist, N., Watrous, J., Mohit, J., Nilsson, R., Cedersund, G. 2022. Validation-based model selection for 13C metabolic flux analysis with uncertain measurement errors. *PLOS Computational Biology*, 18(4): e1009999.

Sundqvist, N., Sten, S., Engström, M., Cedersund, G. 2022. Mechanistic model for human brain metabolism and the neurovascular coupling, *PLOS Computational Biology*, 18(12):e1010798

Sung, J. H., Esch, M. B., Prot, J. M., Long, C. J., Smith, A., Hickman, J. J., Shuler, M. L. 2013. Microfabricated mammalian organ systems and their integration into models of whole animals and humans. *Lab on a Chip*, 13(7): 1201–1212.

Tao, F., Zhang, M., Nee, A. Y. C. 2019. *Digital twin driven smart manufacturing*. Academic Press.

Tay, A., Pavesi, A., Yazdi, S. R., Lim, C. T., Warkiani, M. E. 2016. Advances in microfluidics in combating infectious diseases. *Biotechnology Advances*, 34(4): 404–421.

Van Den Berg, A., Mummery, C. L., Passier, R., Van der Meer, A. D. 2019. Personalised organs-on-chips: Functional testing for precision medicine. *Lab on a Chip*, 19(2): 198–205.

van der Helm, M. W., Henry, O. Y., Bein, A., Hamkins-Indik, T., Cronce, M. J., Leineweber, W. D., Odijk, M., van der Meer, A. D., Eijkel, J. C., Ingber, D. E., van den Berg, A. 2019. Non-invasive sensing of transepithelial barrier function and tissue differentiation in organs-on-chips using impedance spectroscopy. *Lab on a Chip*, 19(3): 452–463.

Wang, Y. I., Carmona, C., Hickman, J. J., Shuler, M. L. 2018. Multiorgan microphysiological systems for drug development: Strategies, advances, and challenges. *Advanced Healthcare Materials*, 7(2): 1701000.

Wang, Z., Samanipour, R., Kim, K. 2016. Organ-on-a-chip platforms for drug screening and tissue engineering. *Biomedical Engineering: Frontier Research and Converging Technologies*, 209–233.

Yang, Y., Fathi, P., Holland, G., Pan, D., Wang, N. S., Esch, M. B. 2019. Pumpless microfluidic devices for generating healthy and diseased endothelia. *Lab on a Chip*, 19(19): 3212–3219.

Zhang, B., Korolj, A., Lai, B. F. L., Radisic, M. 2018. Advances in organ-on-a-chip engineering. *Nature Reviews Materials*, 3(8): 257–278.

Zhang, Y. S., Aleman, J., Shin, S. R., Kilic, T., Kim, D., Mousavi Shaegh, S. A., Massa, S., Riahi, R., Chae, S., Hu, N., Avci, H. 2017. Multisensor-integrated organs-on-chips platform for automated and continual in situ monitoring of organoid behaviors. *Proceedings of the National Academy of Sciences*, 114(12): E2293–E2302.

Židek, K., Piteľ, J., Adámek, M., Lazorík, P., Hošovský, A. 2020. Digital twin of experimental smart manufacturing assembly system for industry 4.0 concept. *Sustainability*, 12(9): 3658.