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DIGITAL TWINS IN PHARMACEUTICAL AND BIOPHARMACEUTICAL MANUFACTURING: A COMPREHENSIVE REVIEW

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ABSTRACT

Digital twin (DT) technology has become a significant advancement in smart manufacturing and is increasingly being adopted in pharmaceutical and biopharmaceutical industries under the concepts of industry 4.0 and pharma 4.0. A digital twin generates a synchronized virtual image of physical manufacturing system that continuously exchanges in real time information for process monitoring, prediction and optimization. This review discusses the architecture and framework of digital systems including physical components, virtual models, and data management platforms. It explains the functional architecture and interactive mapping of DT-based protection systems and highlight the role of supporting technologies such as Internet of Things (IoT), process analytical technology (PAT), cloud computing, machine learning, and manufacturing execution systems. Using digital twins in pharmaceutical production for process design, quality control, predictive maintenance, material tracking and continuous manufacturing is also presented. different modelling approaches including mechanistic, data driven, and hybrid models are discussed along with their significance in process optimization and decision making. Furthermore, the review investigates the application of digital twin technology in biopharmaceutical production as well as its ability to raise product quality and production efficiency. challenges associated with implementation such as data security commerce system integration computational requirements and regulatory compliance are also addressed. finally further development including artificial intelligence (AI), machine learning (MI), edge computing, blockchain technology and cloud-based DT systems are highlighted. digital twin technology offers significant opportunities for improving pharmaceutical manufacturing efficacy reliability and product quality, making it a potentially useful tool for smart manufacturing systems of the future.

KEYWORDS: Digital Twin Technology, Industry 4.0, Pharma 4.0, Internet Of Things (IoT), Process Analytical Technology (PAT), Artificial Intelligence, Machine Learning (ML), Cloud Computing.

1. INTRODUCTION

Acceptance of industry the pharmaceutical manufacturing sector is going through a major upheaval because 4.0 concepts and smart manufacturing frameworks.[1-4] Conventional manufacturing system mostly depend on offline quality testing, through batch documentation and post production verification procedures.[6] These conventional approaches limit real time process visibility and delay corrective decision making. Digital twin technology introduces a new paradigm by enabling the creation of synchronized virtual duplicates of real industrial processes.[2,7] These virtual system may simulate process behaviour, forecast quality attributes and yellow closed loop optimization strategies.[7] Originally developed in aircraft engineering for life cycle management and system performance monitoring, digital twin concepts have evolved into complex industrial applications.[8-10] Digital twin adoption in pharmaceutical manufacturing aligns well with Continuous manufacturing (CM), quality-by-design (QbD), and pharma 4.0 initiative by enabling proactive quality assurance, enhance your process transparency, and real time operational intelligence.[11-13] Despite increasing interest from business and academics, large scale deployment of digital twin platform is still hampered by organizational integration problems, regulatory acceptability limitations under technology maturity gaps.[14] Therefore it is essential to methodically evaluate both current development and opportunities for future advancement.

2. Frame work for Digital twins

Three interconnected layers make up a digital twin system: the data management infrastructure, the virtual modelling layer and the physical layer. These components work together to enable constant synchronization between actual manufacturing process and 3 digital counterparts.[8,15]

2.1 Physical Components

The real industrial environment is represented by the physical layer, which is made up of sensor networks, automation control system, production equipment, and instrumentation.[15] Temperature, pressure, flow rate, and equipment performance indicators are among the vital operating parameters that are continuously obtained through the use of standardized industrial communication protocols such as OPC-UA, TCP/IP, MQTT and modbus.[16,17] Advanced process analytical technology (PAT) tools and soft sensor system enable real time measurement of critical quality characteristics (CQAs) that cannot be directly achieved with conventional hardware sensor.[18,19] These analytical tools provide continuous comprehensive of material attributes and product quality parameters. For further processing, model integration and visualization the collected datasets are transmitted to centralised data historians and cloud based repositories.[20-25]

2.2 The Virtual Part

The virtual layer is made up of who computational models design to replicate the dynamic behaviour of real manufacturing processes. These models Chennai enable simulation- driven analysis optimization based decision support and predictive performance evolution [26-28].

Three primary modelling approaches are commonly employed in digital twin environments:

- Mechanistic models, which are grounded in physical and chemical principles, provide strong interpretability and theoretical robustness despite requiring substantial computers resources.[28-30]
- Data driven models, which are developed using the statistical techniques and machine learning algorithms, enable

rapid prediction and scalability even though their interpretability is sometimes limited.

- while maintaining a decent degree of computational efficiency, hybrid models which integrate mechanistic knowledge with data drive learning techniques offer improved prediction accuracy.[31-34]

  Complex Digital Twin models may now be executed extremely quick thanks to the availability of high-performance computer systems and cloud computing infrastructure, which makes practical implementation in industrial setting variable.[37-39]

2.3 Platform for Data Management

The digital twin system's physical and virtual components can communicate securely and continuously thanks to the data management layer.[15] This architecture includes database system, cloud service, industrial IoT platform and visualization interfaces. Commercial cloud platform like an Amazon Web Services (AWS), Microsoft Azure, Siemens mindsphere and predix provide scalable data streaming, storage and analytical capabilities [40,41]. SQL and NoSQL database architectures are used to manage both organized and unstructured manufacturing datasets. With visualization dashboards, engineers and operators may keep an eye on production performance in real time and model-based forecast. Strong cybersecurity protections are included into the data layer to protect critical pharmaceutical production data from unauthorized access, cyberthreats and data breaches.[42-45]

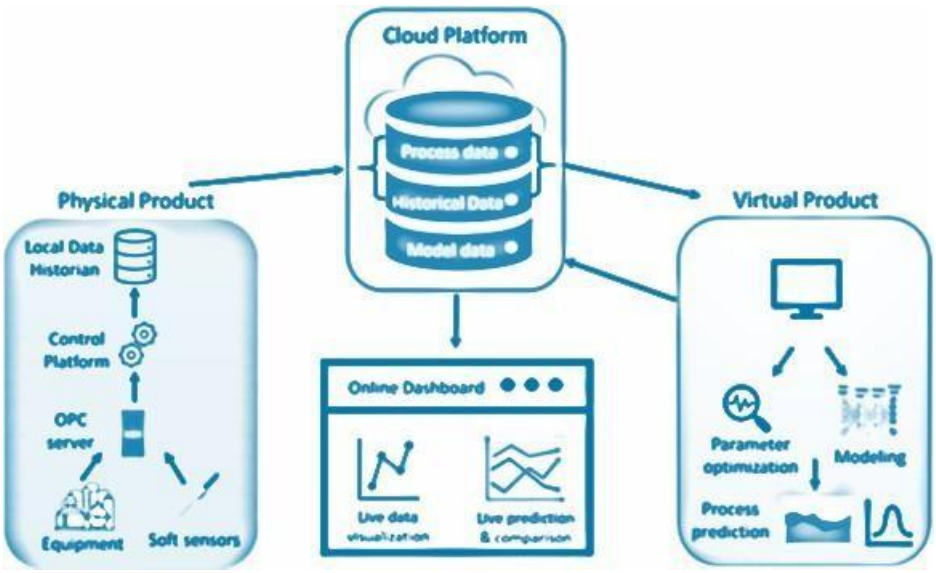

Figure 1: Shows the data management platform, virtual component, and physical component of a general digital twin (DT) framework.

Digital Twin-Based Production System: Functional Architecture and Interactive Mapping

The entire functional architecture and the interactive mapping of a Digital Twin (DT)- based production system, mostly used in industrial and pharmaceutical manufacturing settings, are shown in figure. In order to build a smart and intelligent manufacturing environment, several systems and including conceptual design, production execution system, information services, simulation systems and physical equipment connect with one another.[46] The digital twin, located in the centre of the figure, serves as the systems virtual brain and primary control unit. The Digital Twin is constantly interacting with several supporting components, including the Internet of Things, robot libraries, end-effector libraries, general model libraries, and specialized model libraries. The Physical system and its virtual representation are connected in real time as a result of this interaction.[47] The Digital Twin collects data from the physical world, evaluates it,

forecast behaviour in the future, and transmits optimum choice back to the physical system for improved performance. Rapid decision-making is the made possible by this constant information interchange, which also improves system responsiveness in general.[48] Real-time monitoring aids is spotting the equipment malfunctions under process variations before they become serious problems. The digital Twin's sophisticated analytical algorithms can enhance operation effectiveness and optimize production parameters. By evaluating equipment performance and reducing unplanned downtime, the technology also facilitate predictive maintenance. Additionally, in smart production setting, digital twin technology helps to improve product quality, save manufacturing costs, and boost efficacy.[49]

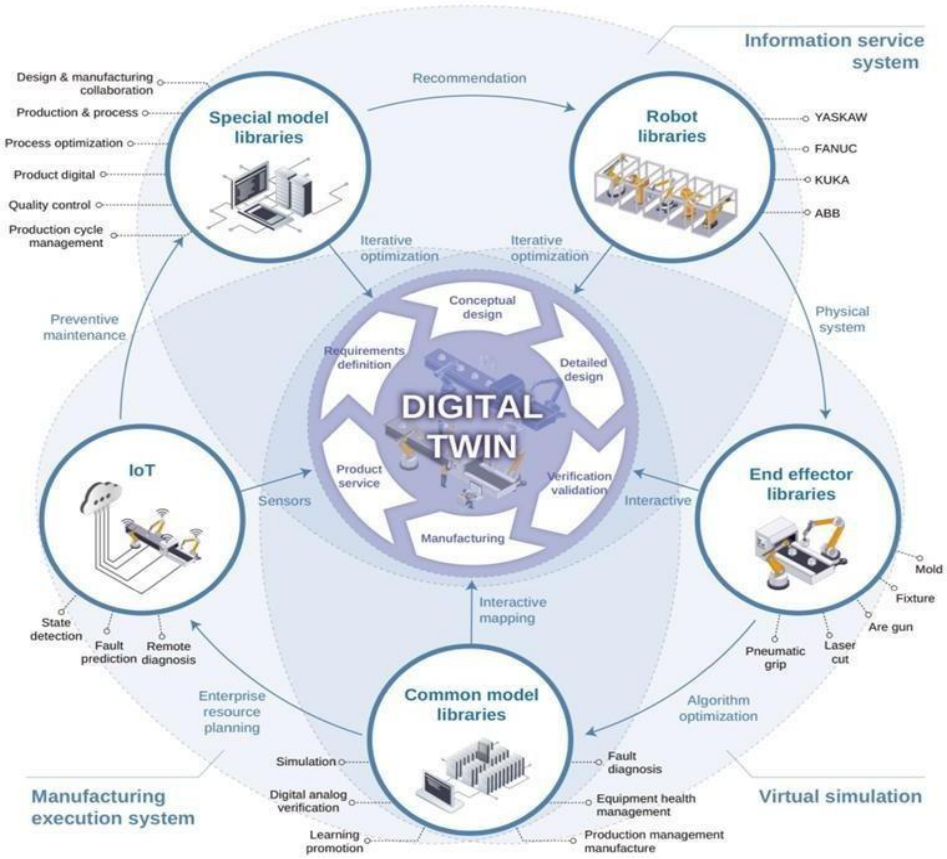

Figure 2: Demonstrates an interactive mapping of a Digital Twin model based on manufacturing execution systems, virtual simulation, and information service systems (Robert libraries → End effector libraries → common model libraries → IoT → special model libraries). Conceptual design, details, production, product service, verification/validation, requirements, and optimization are all included in this mapping.

- **IoT (Internet of Things)** collects data in real time from linked devices and sensors to monitor machine conditions, predict failures and perform remote diagnosis. This helps in predictive maintenance and reduces downtime.
- **Special model libraries** contain models for Production management, quality assurance, predictive maintenance, and process optimization to improve manufacturing efficiency.
- **Robot libraries** store robotic system information and help simulate and optimize robot operation before actual implementation.
- **End-Effector libraries** include tools like grippers, modls and cutters used for specific manufacturing tasks and improve operational efficiency.
- **Common model libraries** contain reusable model for simulation, process planning, fault diagnosis and production

management, reducing development time.

- Digital consist of **physical components**. (machines, sensors, networks) and **virtual components** (Digital models). Both continuously exchange real time information through feedback loop.
- **Manufacturing execution system (MES)** and information system monitor and control manufacturing processes.
- Overall, Digital Twin technology improves pharmaceutical manufacturing by Continuous monitoring, predictive analysis, process optimization, reduce maintenance cost, better fault diagnosis, and improved production efficiency.

3. Digital Twins in Pharmaceutical Production

By enhancing process design and production activities, Digital Twin (DTs) assist smart pharmaceutical manufacture. By forecasting process performance, productivity, and product quality, DT simulations cut down on the time and expense of experiments. DT offers real- time monitoring, analytical and process optimization while in use. Additionally, DT helps with quality control, material tracking, and operator training.[50] PAT, continuous data collecting, QbD, continuous manufacturing, and sophisticated data integration systems are necessary for the successful adoption of DT.[51,52]

4.1. PAT Techniques

Smart pharmaceutical manufacturing is supported by digital twins (DTs) at various phases of product development and manufacture.[51] To conserve time and money during the design phase, DT assist in choosing appropriate production techniques and uses simulations to forecast process performance and product quality. DT continually tracks and evaluates process performance in real-time during the operation stage and offers optimization techniques.[51,52] Through real time simulation DT also serves as an operator training platform. In manufacturing operations, it facilitates material tracking, serialization, and quality control. Real time monitoring, ongoing data collecting and sophisticated data analysis tools are necessary for DT to be implemented successfully. By gathering process and quality data in real time, process analytical technology (PAT) Plays a significant role. Real time monitoring is not possible with conventional techniques like sieve analysis and HPLC.[53] Thus, particle size, mix homogeneity and API content are monitored by PAT instruments including Raman spectroscopy and Near-infrared spectroscopy (NIRS). Together DT and PAT raise Process efficiency, lower manufacturing cost, and enhance product quality.[54,55]

PAT Techniques Involved

S. No	PAT Technique	Principal	Application in Pharmaceutical industry
1	High Performance Liquid Chromatography (HPLC)	Separate and analyse chemical compounds	API concentration analysis and quality testing
2	Raman Spectroscopy	Use the scattered light for molecular analysis	Online monitoring of powder blend process
3	Near Infrared Spectroscopy (NIRS)	Use near infrared light absorption	Blend uniformity, powder density, API concentration prediction
4	Nuclear Magnetic Resonance (NMR)	Use magnetic properties of molecules	Structural and chemical analysis
5	Ultraviolet Spectroscopy (UV)	Measures UV light absorption	Drug concentration measurement
6	Best Infrared Spectroscopy	Use infrared absorption patterns	Identification of pharmaceutical compounds
7	Online Mass Spectroscopy	Measures molecular mass of compounds	Real time process monitoring
8	Focused Beamed Reflectance Measurements (FBRM)	Use laser beam reflection	Particle size distribution easurement
9	High Resolution Camera System	Capture visual particle images	Particle size and shape analysis

4.2. Modeling Processes

Because Digital Twin (DT) technology preliminary relies on data and mathematical models to comprehend, simulate and optimize pharmaceutical production process processes modelling is a critical part of the DT technology.[55] Batch and continuous manufacturing, material property production, process simulation, system analysis, and process control all require different models. By identifying the process deviations, forecasting product quality and streamlining manufacturing process, these models can cut down on development time and expenses.[55,56] Pharmaceutical production uses three main modelling techniques: mechanistic models, hybrid models, and data-driven models. Mechanistic models such as the Discrete Element Method (DEM), Computational Fluid Dynamics (CFD), and Finite Element Method (FEM) are based on mathematical and physical concepts.[57] While CFD and FEM are utilized for fluid flow process like API drying and fluidised bed operations, DEM is primarily used to examine particle mobility under material flow. This techniques demand a lot of processing power even though they yield precise result. Large volume of experimental data are used to create a data-driven models, which use the technique like Monte Carlo methods, multivariate statistical analysis and artificial neural networks (ANN). Due to their lack of physical understanding, these models may yield false finding outside of the available dataset, but they also offer faster predictions and require less computational work.[58-60] Hybrid models reduce computational cost of while increasing prediction accuracy by combining a mechanistic country data-driven approaches population balance modelling (PBM) and PBM-DEM hybrid models, which are frequently employed in blending and granulation procedures, are two examples. These models facilitate quicker drug development and enhance process comprehension.[61,62] Furthermore, flowsheet models incorporate the entire manufacturing process and aid in the creation of process control strategies, sensitivity analysis, design space identification and optimization. The fact that the flowsheet models often operate offline and are unable to dynamically update depending on real time plan data is significant drawback, too. Therefore, one of the biggest obstacles to creating fully functional Digital Twin system in maintaining constant communication between real plants and virtual models.[63]

4.3 Integration Data

Because pharmaceutical manufacturing produces a lot of data through IoT devices, sensors and Critical Quality Attributes (CQS), It is an essential part of the Digital Twin (DT) technology. For precise process monitoring and production, this data must be gathered and prepared to the virtual component in the moment. For the purpose of storing manufacturing data, material attributes, simulation findings and optimum process parameters, a central database is necessary.[20] In accordance with US FDA rules, the database must also adhere to 21 CFR part 11 regulations to preserve data integrity. Using the process control system (PCS) and manufacturing execution system (MES), several research have created integrated data frameworks for pharmaceutical manufacturing.[64-68] Protocols including TCP/IP, OPC, MQTT and HTTPS are used to establish communication between databases and equipment. Data from manufacturing and laboratories can be transferred to cloud databases so that the virtual digital twin can use it for analysis and simulations.[69-71] Process control, product quality and overall production efficiency can all be improved by returning optimized process parameters and corrective actions to the manufacturing system based on simulation results.[20]

4.4 Digital Twin (DT) Opportunities and Challenges

The primary goal of pharmaceutical production is to develop a fully integrated system in which real-time information exchange occurs continually between the virtual model and the actual plant. The virtual component receives to process

data from the physical manufacturing system for ongoing monitoring, analysis, visualization and storage. The digital twin can automatically optimize and regulate process activities based on the data, resulting in a continuously feedback loop that enhance production performance.[72-75] Despite the pharmaceutical industry's adoption of technology such model predictive control, data storage, visualization, Process Analytical Technology (PAT) and continuous monitoring, there are still a number of issues.[4] Process monitoring accuracy is significantly difficulty, particularly in low-dose medication measurement where result may be impacted by calibration issues and external interference. The high computational cost of complicated models like integrated process models, CFD and DEM, which all for cloud computing and high-performance platforms, presents another difficulty. In the Pharmaceutical industry, a lot of a lot of models are static, which means they don't automatically update when new process data become available. For gather forecast accuracy and ongoing update, adaptive and hybrid models are therefore necessary.[74,75] Communication between virtual and physical system is another significant difficulty. Reverse communication for automatic process control is currently restricted, and the majority of existing systems merely move data from the virtual model to the real plant. Another problem with data integration is that different manufacturers utilize different platforms, software and data formats, which makes collaboration challenging. Additionally, because pharmaceutical data is extremely private, cloud-based system raise issues with data storage, service dependability and cybersecurity.[76,77] But these difficulties also present chances for the advancement of more sophisticated digital twin technologies, cyber-physical security techniques, and safe cloud system. The creation and use of digital twin system in pharmaceutical manufacturing are also being supported by regulatory bodies like the USFDA.[78]

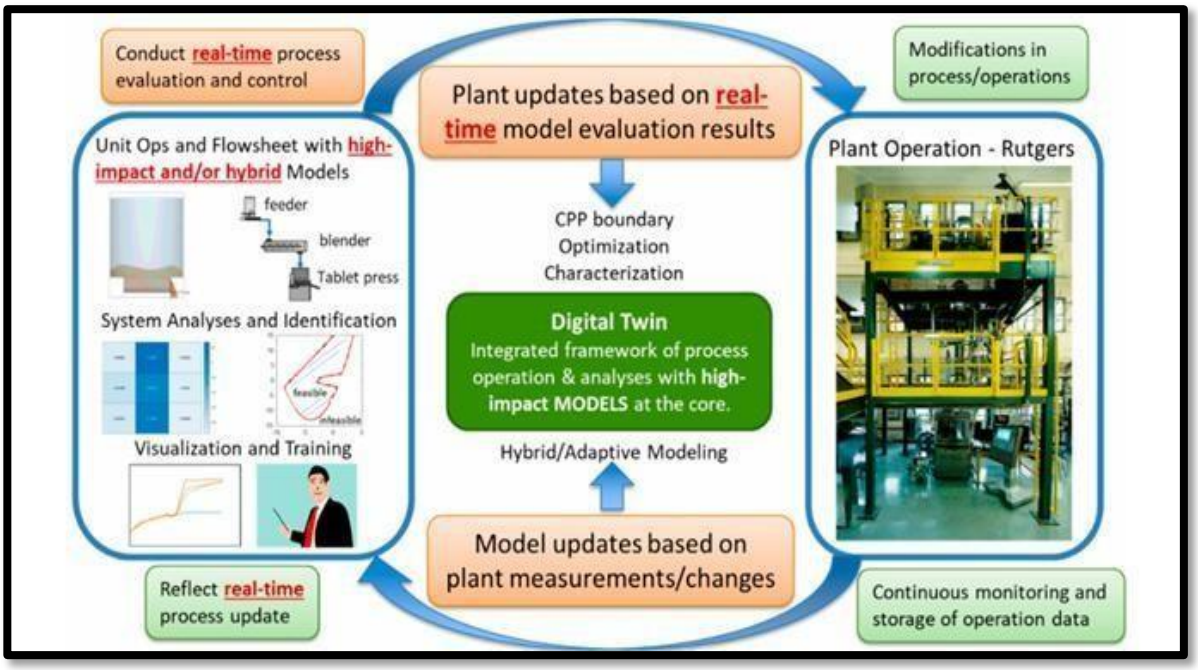

Figure 3: Continuous pharmaceutical manufacturing using a fully integrated DT framework.

4. Digital Twin in Biopharmaceutical Manufacturing

Biopharmaceutical manufacturing system are highly complex because they involve challenges such as improving drug by ability, controlling production variability and regulating cell culture processes.[79] Digital twins (DTs) have emerged as an advanced technology that enhances the production efficiency of biologics, including monoclonal antibodies (mAbs). DTs utilize process models, real-time monitoring systems and Artificial Intelligence (AI)-based hybrid frameworks to

predict optimal operating conditions and determine appropriate harvest timings, thereby reducing batch failure and improving overall manufacturing efficiency.[80] Hybrid DT models, integrate process data, lifecycle management information and expert knowledge by using computational techniques such as Support Vector Machines (SVM). Bayesian networks and deep learning approaches. These integrated models facilitate fault detection, predictive maintenance, and process optimization. However, several challenges still exist, including the integration of legacy manufacturing system with modern DT technologies, stict validation requirement and regulatory concerns. Despite these limitations, DTs offer significant potential in biopharmaceutical manufacturing by enabling real-time monitoring, improved process control, predict maintenance and Sustainable production practice aligned with Industry 4.0 principles.[81]

5.1. Production of Biopharmaceuticals

In biopharmaceutical production, Digital Twins (DTs) generate a virtual model of the manufacturing process to enhance operational effectiveness and decision making. During these production phase, the digital twin continuously gathers real-time data from the sensor and Process Analytical Technology (PAT) instruments and send it to the virtual system. The virtual system forecasts future process behaviour under transmits optimized instructions back to the physical manufacturing system after analysing process parameters like temperature, pH, nutrient concentration and product quality features.[82] Process optimization and forecast accuracy are enhanced by hybrid models that incorporate machine learning (ML) and artificial intelligence (AI). By identifying equipment issues before they happen, this interaction establishes a continuous feedback loop that helps find process bottlenecks, shorten manufacturing cycle times, increase product output and assistive predictive maintenance. Additionally, DT enhances automated documentation, regulatory compliance, traceability and quality assurance.[83]

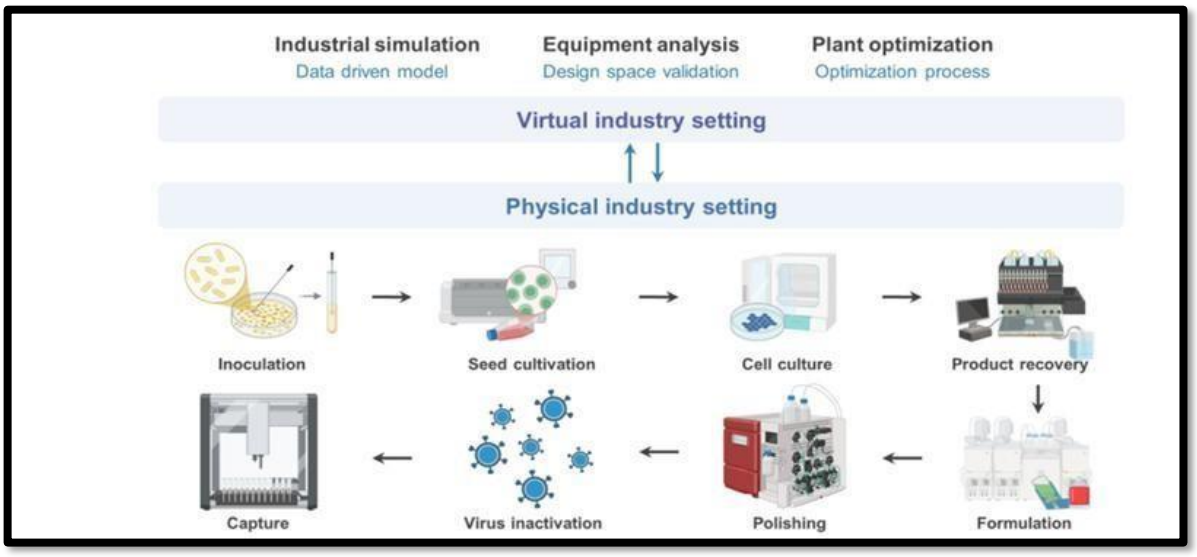

Figure 4: The application of digital twin (DT) technology in biopharmaceutical manufacturing is shown in Figure 4, Where a virtual industry environment is constantly linked with a physical industry setting to enhance decision making and production efficiency. The virtual environment, seen in the upper portion of the figure, uses data driven models and design-space validation to carry out to industrial simulation, equipment analysis and plant optimization. The physical manufacturing process is depicted in the lower section. It consists of multiple production steps, including inoculation, seed cultivation, cell culture, product recovery, capture, virus inactivation, polishing, and formulation.

Table 1: Different software available for Digital Twin (DT) implementation along with their developers, Specific application, software categorization based on usage and company websites. souces: https://doi.org/10.1016/j.ijpx.2025.100409

No.	Software	Developer	Use	Category	Website
1	Ability™	ABB	Industrial platform	IoT	https://global.abb/topic/ability/en
2	AnyLogic	AnyLogic	Business application	Simulation	https://www.anylogic.com
3	Azure DTs	Microsoft	Simulation	IoT	https://azure.microsoft.com/en-us/products/digital-twins
4	BIM 360	Autodesk	Building information models	BIM	https://www.autodesk.com/bim-360
5	Digital Sol	DNV GL	Supply chain, product assurance	Analytics	https://www.dnv.com/about
6	DTs	Emerson Electric	Sensor & optimization	IoT	https://www.emerson.com/en-us
7	DTs	Oracle	Predictive maintenance	IoT	https://docs.oracle.com/en/cloud/paas/iot-cloud/iotgs/oracle-iot-digital-twin-implementation.html
8	DTs	Siemens	Asset performance	IoT	https://www.siemens-advanta.com/capabilities/offers/asset-performance
9	Forge	Honeywell	Digital transformation	IoT	https://process.honeywell.com/us/en/solutions/honeywell-forge-advanced-process-control
10	Insight	AVEVA	Operation optimization	Analytics	https://www.aveva.com/en/products/insight
11	Intergraph	Hexagon	Material management	Visualization	https://hexagon.com/products/intergraph-smart-3d
12	IoT Suite	Bosch	Data analytics	IoT	https://bosch-iot-suite.com
13	IoT Studio	Altair	Data analytics	IoT	https://altair.com/altair-iot-studio
14	Leonardo	SAP	Machine learning	IoT	https://mdpgroup.com/en/blog/what-is-sap-leonardo
15	NX	Siemens	Design and manufacture	Design	https://plm.sw.siemens.com/en-US/nx
16	Predix	GE Digital	Asset & operations performance	IoT	https://www.ge.com/digital/iot-platform
17	Simio	Simio LLC	3D modelling	Simulation	https://www.simio.com
18	Simulia	Dassault Systèmes	Finite element analysis	Simulation	https://www.3ds.com/products-services/simulia/overview
19	Simulink	MathWorks	Model-based design	Simulation	https://www.mathworks.com/products/simulink.html
20	Smart Manufacturing	Rockwell Automation	IoT integration	Automation	https://www.rockwellautomation.com/en-us.html
21	ThingWorx	PTC	Visualization, AR development	IoT	https://www.ptc.com/en/resources/iiot/product-brief/thingworx-platform
22	Twin Builder	Ansys	Modelling	Simulation	https://www.ansys.com/products/platform/twin-builder
23	Unity Reflect	Unity Technologies	BIM model in virtual reality	Visualization	https://unity.com/pages/unity-reflect
24	Watson IoT	IBM	Data analytics	IoT	https://www.ibm.com/cloud/internet-of-things
25	Witness	Lanner	Process modelling	Simulation	https://www.lanner.com/en-gb/technology/witness-simulation-software.html

Table 2: Applications of Digital Twin in Various Industries.

sources: https://doi.org/10.3390/pr8091088

Areas of application	Specific application	Purpose	Component of DT framework with software
Energy production	Steam turbines	Integrates historical data with real-time process to forecast wear/tear and suggest modifications	mponent using predix
Energy production	Wind farm	Integrates historical data to enhance process efficiency and predict maintenance strategies	Virtual component based on General Electric (GE) fleet using predix
Smart product manufacturing	Factory smart floor map	Redesigning manufacturing platforms	Virtual replica of manufacturing floor to optimize location of machinery and sensors
Smart product manufacturer	Digitization of manufacturing of packaging machines	Redesigning product to improve production efficiency and digitize overall process design	Virtual model using Siemens mechatronics concept designer
Aviation industry	DT of next-generation aircrafts	Aircraft structural health management and assessment of potential damage analysis	Virtual replica of airplanes using GE's predix software platform
Aviation industry	Airframe DT simulator (ADT)	Training and engineering solutions	Virtual simulator using GE's predix software
Aerospace industry	DT of outer-space vehicles	Replication of health maintenance problems and monitoring for safety and reliability	Virtual replica of vehicle onboard integrated system
Automotive transportation	DT of cars	Prediction and assessment of maintenance issues for improving automobile durability	Virtual replica of automobiles
Automotive transportation	Automated transport vehicles	Vehicle simulation for safe automated long-distance transportation	Dassault system using digital control system
Healthcare industry	Virtual replica of patients	Surgical operation training and health monitoring using sensors	Virtual component developed using simulated environment
Healthcare industry	Living heart project	3D model of human heart for blood circulation analysis and pharmacokinetic/ pharmacodynamic (PKPD)testing of medicines	Virtual model using finite element-based modelling environment
Infrastructure planning	City planning	Construction of smart, sustainable city infrastructure	Visual digital replica using information communication technology

6. Challenges and Considerations

6.1. Privacy and Data Security

Large volumes of sensitive data must be gathered and processed in order to use digital twin technology. In order to preserve privacy and guarantee system security, it is crucial to safeguard sensitive data, including intellectual property and patient related information.[84]

6.2. Large initial outlay

Digital twin technology adoption necessitates is substantial upfront investment. This covers the price of high-performance computing infrastructure, software platforms, data storage system and sophisticated sensors.[84]

6.3. System integration complexity

It can be difficult to integrate digital twin technology into current industrial systems, particularly when older or legacy

system are involved. Compatibility with current IT infrastructure and appropriate customisation are crucial aspect to take into account.[84]

6.4 Regulatory aspects

The FDA, EMA and other international agencies have said regulatory requirement that must be followed while implementing digital twins. Manufacturers must provide appropriate traceability, data integrity and adherence to legal requirements.[84]

7. Future Trends And Developments

7.1. Combining machine learning with Artificial Intelligence

Predictive capacities can be enhanced by interacting digital twins with artificial intelligence (AI) and machine learning (ML). This technologies can assist a system with intelligent decision-making real time data analysis and automated manufacturing process optimization.[85]

7.2 Applications of Edge Computing

Real time data processing at the source like factory sensor can be supported by interacting edge computing with digital twins. This method can lessen the strain on central servers and facilitate quicker decision-making.[85]

7.3 Using Blockchain To Enhance Traceability

Digital twin and blockchain technology can be combined to provide safe unchangeable documentation of pharmaceutical manufacturing processes enhancing data integrity and traceability.[85]

7.4 Digital Twin System Based On The Cloud

Particularly in international pharmaceutical firms with numerous manufacturing sites, cloud - based digital twin solutions can offer increased scalability, flexibility and teamwork.[85]

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