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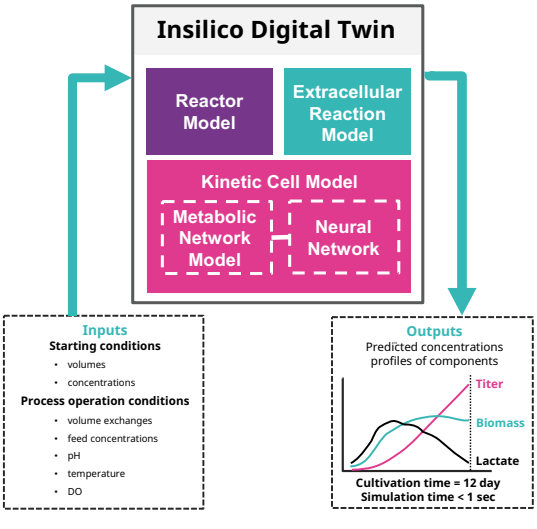

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Building intelligent processes for Pharma 4.0

How to develop a smart cell culture bioreactor

By Shilpa Nargund, Managing Director, Yokogawa Insilico Biotechnology

Market needs for cheaper, safer and better-quality drugs are driving digital transformation within the pharmaceutical industry.

The amalgamation of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines and Industry 4.0 has resulted in a new era called “Pharma 4.0.” A key piece to achieving Pharma 4.0 is the enabling of smart manufacturing. This involves developing intelligent processes that can self-adapt.

Smart manufacturing is possible due to advances in technologies such as artificial intelligence (AI), the Industrial Internet of Things (IIoT), sensors, robotics, and virtual reality. The core driver, however, is data. When data is converted to decisions that are automatically executed, we achieve ‘smart’ manufacturing processes.

To convert data into decisions, we need to build models that learn the hidden rules in the data. These models must accurately mimic the behavior of the manufacturing process. The most sophisticated models can predict the outcome of a process and prescribe desired changes to it. Such models are called digital twins. A digital twin is a virtual representation of a physical object that reacts to interventions in a manner that is identical to its physical counterpart. Most digital twins rely on machine learning methods to learn hidden rules in the data. However, it is best to build hybrid models that combine mechanistic knowledge with data-driven knowledge.

Once a digital twin is prepared, we must enable it to automatically execute its prescriptions on the manufacturing process. This means that the twin's outputs need to be converted into control actions by an intermediary. The twin also needs to obtain feedback from the manufacturing process in real-time using this intermediary. Developing these intermediary communicators between the digital and physical counterparts is the last crucial step in endowing 'smartness' to the manufacturing process. Further, in the pharma industry, all components of the smart manufacturing process must comply with ICH guidelines.

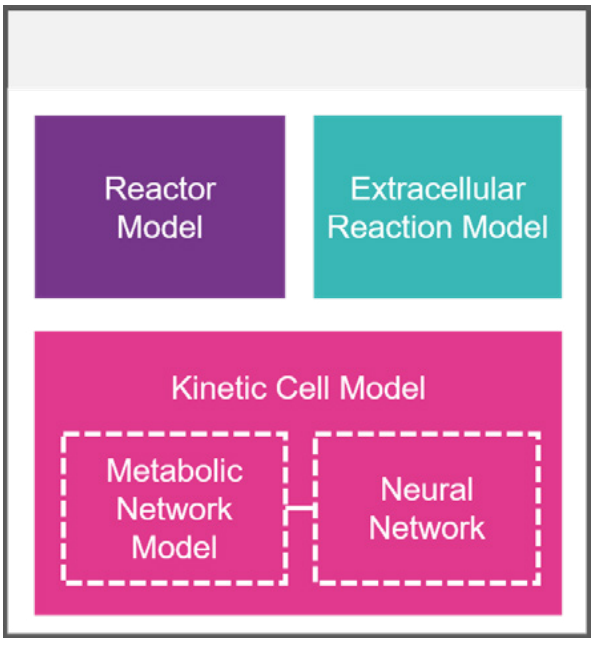

Exhibit 1. Digital twin hybrid model

In the next few sections, we will showcase our approach to developing a 'smart' cell culture bioreactor for biomanufacturing.

BUILDING A DIGITAL TWIN OF A BIOREACTOR

The digital twin predicts the concentration profiles in the bioreactor during a virtual experiment. In our approach, we have built a hybrid model that combines three models – the Reactor Model, the Extracellular Reaction Model, and the Kinetic Cell Model.

The Reactor Model describes batch, fed-batch, or continuous processes by accounting for the changes in volumes and component concentrations in the bioreactor vessel that result from the inlet (feeds, base, antifoam, etc.) and outlet streams (samples, cell bleed, harvest, etc.). The Extracellular Reaction Model tracks concentration changes due to abiotic reactions such as degradation of glutamine in the cell culture media.

The Kinetic Cell Model tracks concentration changes in the bioreactor that result from cell metabolism and growth. This is arguably the most critical part of the digital twin. Here, a genome-scale metabolic network model is combined with an artificial neural network. The time-series data from cell culture processes (e.g. viable cell density, titer, amino acids, lactate, ammonia, etc.) is used in two ways when training the digital twin. It is first used by the metabolic network model to identify the active

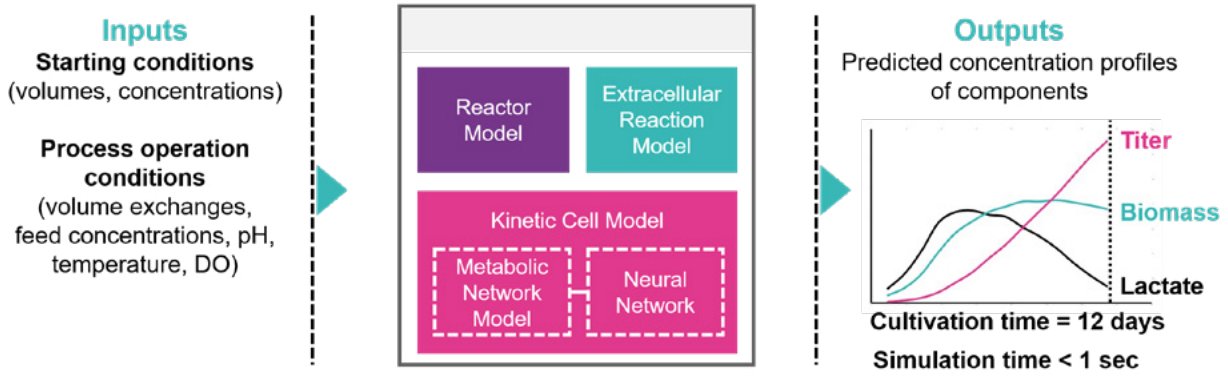

Exhibit 2. Digital twin hybrid model inputs and outputs

metabolic pathways in the cells by methods such as flux balance analysis. Thus, the known rules such as the law of conservation of mass and biochemical pathways are explicitly modeled. The second way we use the data is to allow the neural network to learn the kinetics of the active metabolic pathways. The reader may appreciate that the most difficult challenge when modeling cell metabolism is the estimation of the rates of metabolic reactions. Our hybrid approach ensures that the neural networks are burdened only with this task. This helps us build accurate digital twins with less data than would otherwise be required.

VIRTUAL EXPERIMENTS WITH THE DIGITAL TWIN

Once the digital twin is trained, it can be used for virtual experiments at any stage of the drug substance life cycle. To conduct a virtual experiment, the digital twin needs inputs such as the starting conditions and the process operating conditions. These include information on concentrations of basal and feed media, feeding and sampling volumes, feeding and sampling timepoints, and set points of pH, temperature, and dissolved oxygen. At every time-point, the twin calculates the changes in concentrations due to process operation, extracellular reactions, and cell metabolism and growth.

The outputs of the digital twin are the time-series concentrations of key components in the bioreactor such as biomass, product titer, lactate, amino acids and ammonia. The twin can simulate a 12–14-day process in less than one second. We can conduct thousands of virtual experiments in a few hours. Further, we have built Prediction Apps that conduct these virtual experiments intelligently. For example, if the objective of an experiment is to maximize product titer, the Prediction App uses an optimization algorithm to search media compositions and feeding schemes that lead to the highest product titer.

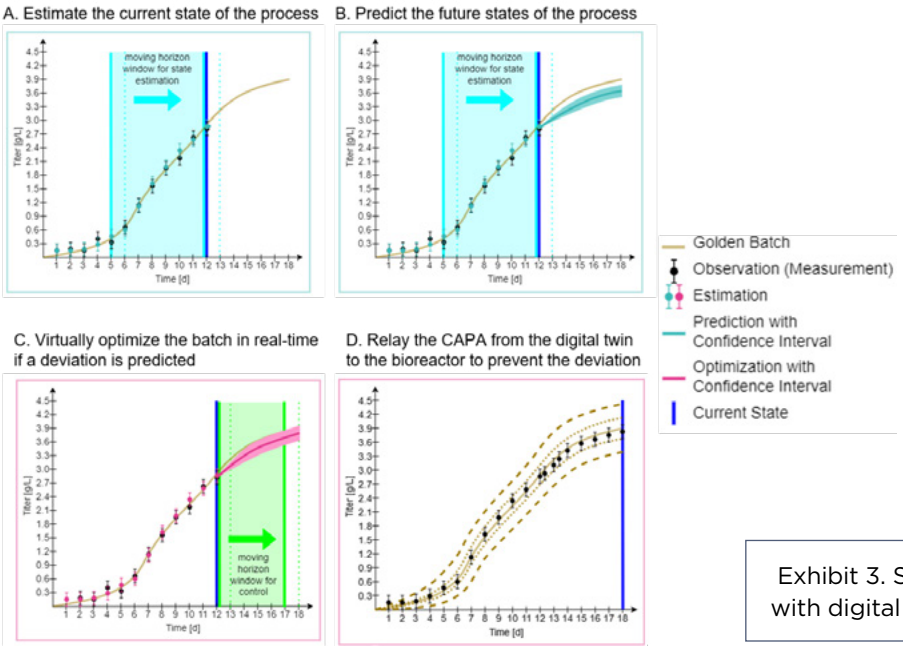

Exhibit 3. Steps in communication with digital twin

VALIDATING A DIGITAL TWIN

When deploying a digital twin for real-time model predictive control of the cell culture process, it needs to be validated. The regulatory guidelines on validation of machine learning based models are not yet finalized. However, we expect that the following approach would be suitable. The validation must be carried out in two steps. In the first step we aim to establish the accuracy of the digital twin and, in the second step, we aim to continuously verify the robustness of the twin.

To build an accurate digital twin, it is necessary to train it with cell culture data that has variability. This helps the twin learn the dynamics of good and bad cell culture processes and improves its ability to extrapolate from the known knowledge space. Since such variability is best achieved during the early stages of process development, it is necessary to train the digital twin using data from these stages. The rewards of building the digital twin at the earlier stages are also higher. We estimate that a company can save between eight and 15 months of Chemistry, Manufacturing and Controls (CMC) time by iteratively developing and using the digital twins through the stages of clone selection, process development, scale-up, and process characterization. The twin retains the knowledge from data acquired at each stage to compound its accuracy. Thus, the first step of the validation is achieved before deploying the twin for model-predictive control of manufacturing processes.

In the second step of validation, the digital twin is continuously verified for robustness. This does not mean that the validation

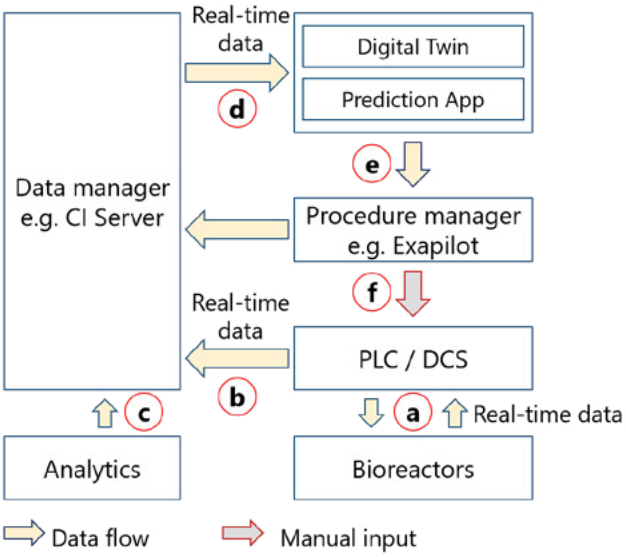

Exhibit 4. Data flow during model predictive control of a bioreactor.
a), b), c) on-line and off-line process data is transferred to the data manager. d) The data is transferred from the data manager to the Digital Twin and its Prediction App. e) The CAPA from the digital twin is relayed to the procedure manager. f) the operator reviews the CAPA and accepts or rejects it through procedure manager. f) the CAPA is sent to the PLC/DCS of the bioreactor which controls the feed valves.

must occur online or in real-time with a manufacturing batch. It means that, over the lifetime of the digital twin as data from manufacturing batches is accrued, the twin should be re-trained with it. This may be done semi-annually or annually. The re-trained twin must be validated offline for robustness. This requires development of standard tests that provide known outputs after every re-training of the digital twin. The digital twin can be updated with the re-trained twin once the offline validation is completed.

ACHIEVING COMMUNICATION BETWEEN THE BIOREACTOR AND ITS DIGITAL TWIN

To complete the 'smart' bioreactor, it must be able to communicate with its digital twin in real-time. As illustrated in Exhibit 3, this entails a few steps. The cell culture process in this example takes 18 days and is currently on day 12. The first step for the digital twin is to estimate the current state of the process using the data acquired thus far. Exhibit 3A shows the measured and simulated concentrations of product titer up to day 12. In the second step, the digital twin estimates the future states of the process (Exhibit 3B). If a deviation from the golden batch is predicted, the digital twin carries out an optimization of the process in real-time and derives a corrective action (Exhibit 3C). In this example, the product titer is predicted to be lower than the golden batch and the digital twin optimizes the feed volume to prevent the dip. Finally, this corrective action is relayed from the digital twin to the bioreactor.

Enabling communication between the bioreactor and its digital twin requires intermediary information managers. Yokogawa is building a prototype of this system using

digital solutions for data management and procedure management. Exhibit 4 shows the communication flows. A data manager provides real-time data transfers between the bioreactor and the digital twin. If the twin predicts a deviation, it relays the corrective action and preventive action (CAPA) to the procedure manager. In the current prototype, the operator has an option to accept or reject the CAPA through the procedure manager. This is the only manual step in the system. It can also be automated in the future. The procedure manager would transmit the control action to the programmable logic controller (PLC) or distributed control system (DCS) that controls the bioreactor.

SUMMARY

Smart manufacturing relies heavily on building self-adaptive processes. In practice, this means that a process should be able to detect and prevent deviations automatically. In this article, we have showcased an approach to developing a 'smart' bioreactor for manufacturing of biologics. The critical steps in achieving advanced process control include building an accurate digital twin of a bioreactor, validating it, and establishing communication between the bioreactor and its digital twin. Several of these steps are already mature and the industry is making rapid progress toward realizing 'smart' bioreactors for smart manufacturing.

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