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Artificial intelligence applications for fault detection and diagnosis in pharmaceutical bioprocesses: a review

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Because of increasing demand and strict regulations, pharmaceutical manufacturers encounter significant hurdles in achieving high productivity while ensuring normal process states. Variability in raw materials and operational disturbances can lead to deviations from normal operating conditions that result in decreased productivity. The implementation of smart fault detection and diagnosis (FDD) techniques is crucial for attaining acceptable productivity and ensuring process safety. In this review, we identify the major challenges of smart FDD in pharmaceutical processes, and we discuss future opportunities and new perspectives.

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Introduction

Optimization of bioprocesses is crucial for ensuring the quality, efficiency, and safety of final pharmaceutical products. Fault detection and diagnosis (FDD) are key tasks for ensuring process optimality by offering the means to identify, mitigate, and prevent deviations that could compromise product integrity or production efficacy. Traditional methods for fault detection have often relied on rule-based or multivariate statistical techniques, which, while effective in certain scenarios, can struggle to cope with the complexity and variability inherent in bioprocesses [1].

Pharmaceutical processes are mostly conducted in batch or fed-batch modes to minimize contamination risks [2]. By evolving through a wide range of operating conditions, batch operations exhibit highly nonlinear behavior. This stands in contrast to continuous processes, where the system typically operates in the neighborhood of a specific steady state, thus permitting linear modeling approximations.

In recent years, significant focus has been placed on advancing global methodologies for real-time process monitoring, particularly after the introduction of the process analytical technology guidance by the Food and Drug Administration [3]. Artificial intelligence, characterized by its ability to automatically learn hierarchical representations from data, has revolutionized the field of FDD [4] in many industries. Research on deep learning models, with their capacity to extract intricate nonlinear patterns from large datasets, has shown great promise in enhancing the accuracy and robustness of fault detection systems within pharmaceutical bioprocesses. Deep learning applications involve training deep learning models, such as convolutional neural networks (CNNs) [5], recurrent neural networks (RNNs) [6], or hybrid architectures [7], on large datasets comprising various process variables, sensor readings, and other relevant data sources. While there is active research on these approaches, the adoption of deep learning by the pharmaceutical industry is still limited.

Because of the high sensitivity of cellular organisms to changes in operating conditions, for example, changes in temperature, pH, oxygen, and nutrient levels, bioprocesses experience deviations from normal operating conditions that can be referred to as 'faults.' While minor variations or external influences can be effectively regulated by common controllers, for example, Proportional–integral–derivative controllers, significant deviations from the norm may require operator intervention or even temporary shutdown for thorough inspection. Accordingly, a fault can be defined as any factor that disrupts the process by driving it beyond its normal operating conditions, thus requiring external intervention to restore equilibrium [8].

Thus, it is crucial to define the normal operation of a bioprocess toward the implementation of a fault detection algorithm. While normal operation should be defined in terms of both productivity and quality, the lack of accurate measurements of these properties makes accurate classification between normal and faulty states a challenging task. For example, productivity assessments by Enzyme-linked immunosorbent assay, High-performance liquid chromatography, and other titer analyses may introduce significant noise, potentially undermining the efficacy of models aimed at distinguishing between normal and faulty samples. This often motivates the preference of unsupervised over supervised learning techniques [9]. Unsupervised methods refer to techniques where the model learns patterns and structures in data without explicit use of samples labeled according to the property defining normal operation, for example, the desired quantity or quality of the product. While in supervised learning, the model is trained on inputs and labeled outputs, unsupervised methods focus on extracting meaningful representations or features from the input data itself. Furthermore, since pharmaceutical processes frequently entail unknown faults due to lack of measurements, unsupervised algorithms are preferred as they can identify and diagnose faults without prior knowledge of their occurrence [10].

This paper provides a review of artificial intelligence techniques applied in FDD over the past five years, specifically within pharmaceutical bioprocesses. While other recent review papers explore related subjects such as machine learning in general chemical processes [11•] or the role and use of big data in biochemical processes [12], their focus is not on AI-based FDD algorithms for pharmaceuticals as in this review. We identify the challenges inherent in implementing deep learning approaches within the context of pharmaceutical bioprocesses, such as data scarcity, interpretability of results, and regulatory compliance. By addressing these challenges and proposing potential solutions, this review seeks to contribute to the advancement of deep learning methodologies tailored specifically for FDD in the manufacturing of pharmaceuticals.

Fault detection and diagnosis

Fault detection

The detection of a fault is based on a statistically significant boundary between normal and faulty data. In practical applications, data-driven fault detection typically involves several steps: i) a fault detection model is trained with data collected under normal operating conditions; ii) control limits, such as Hotelling's T^2 and mean reconstruction error Q–statistic, are calculated based on the model; iii) during online operation, the developed FDD model is fed new sample's data and compares its response to the established control limits; and iv) if T^2 or Q–statistical bounds exceed the corresponding control limit, the new sample is flagged as a fault.

Multivariate statistical algorithms

Multivariate statistical algorithms are widely applied through commercial software (SIMCA [13]) and are renowned for their ease of implementation. Principal component analysis (PCA) and partial least squares (PLS) are the most common multivariate statistical algorithms for batch process monitoring in the industry. Typically, they utilize Hotelling's T^2 statistic and Q–statistic to detect faults. However, because of the nonlinear and dynamic nature of data from chemical processes, linear PCA and PLS algorithms are not accurate enough. Hence, kernel-based and dynamic-based methods such as kernel PCA, kernel PLS, dynamic PCA, and dynamic PLS have been developed to enhance performance. Also, because of the prevalent batch or semibatch nature of pharmaceutical processes, multiway-PCA (MPCA) and multiway-PLS (MPLS) methods are commonly utilized in practice [14••]. Additionally, nonlinear PCA and nonlinear PLS algorithms, which are based on autoencoder (AE) neural network structures, have also been utilized for batch process monitoring to capture the dynamic and nonlinear aspects of the process [14,15••]. The following section provides more details about these algorithms.

Deep learning algorithms

Deep neural networks (DNNs) have the ability to uncover inherent nonlinear and dynamic patterns and hierarchical structures, often resulting in superior performance than traditional machine learning techniques such as multivariate statistical methods.

Different novel neural network architectures have been proposed that are particularly useful for fault detection in nonlinear dynamic problems, for example, multilayer neural networks, AEs, and RNNs, such as long short-term memory (LSTM) [15••] and gated recurrent units [16••]. Specifically, CNNs have proven adept at capturing process nonlinearity with heightened accuracy [17•]. Generative adversarial networks (GANs) have emerged as a tool for addressing data scarcity by generating realistic synthetic data for training [18–21,22].

Hybrid models

While neural networks have high interpolating capability, they are less accurate at generalizing behavior, that is, predicting outputs for input values that are very different from those used for training. Gray-box or hybrid models combine both mechanistic and data-driven modeling techniques to improve predictive capabilities and reduce reliance on training data [23]. These hybrid models integrate mechanistic and data-driven components either in serial or parallel architectures [24]. Mechanistic models describe fundamental conservation

Table 1

Summary of reviewed papers.

Model	Purpose	Results	Ref.
PCA	FDD in a pharmaceutical drug manufacturing	Addressing batch process challenges: drifting; overlapping; imbalanced data.	[29]
MPCA, MPLS MPLS-AE	FDD in a penicillin batch process	The MPLS-AE model shows superior accuracy compared with others.	[14••]
Long short-term memory autoencoder (LSTM-AE)	FDD in a penicillin batch process; Sanofi *B. pertussis* vaccine manufacturing process	Exhibits a clear accuracy improvement over linear or nonlinear techniques that do not explicitly consider dynamic behavior.	[15••]
Multiway Kernel Entropy Independent Component Analysis (MKEICA)	FDD in a penicillin batch process; an actual bioprocess	To address the challenges of nonlinear and non-Gaussian traits in batch processes and diagnose faults using nonlinear contribution plots.	[30]
Affinity propagation broad learning system (AP-BLS)	FD in a penicillin batch process	To develop a multistage monitoring framework integrating AP and BLS, surpassing AP-PCA, AP-ICA, AP-LSTM.	[31]
Supervised deep convolutional autoencoder (CNN-AE)	FDD in a penicillin batch process	The CNN-AE model significantly outperformed the PLS-DA model in the optimal integration of FDD with process design.	[17•]
Canonical variate analysis (CVA)	FDD in a granulation process	Addressing nonlinearity in dynamic processes for future automated FDD.	[32,33]
Multiphase enhanced high-order information extraction (MEHOIE)	FD in a penicillin batch process; a microbial bioprocess	Addressing feature extraction challenges with a higher number of samples than features, surpassing PCA and ICA.	[34]
AEs, K-means clustering, and multi-input neural networks	FDD in rolling elements bearings in an industrial pharmaceutical process	To propose a scalable framework for automated prediction of degradation stages in rolling-element bearings, offering reliable predictions.	[35]
Differential recurrent neural network (DRNN)	FD and QP in a penicillin batch process	Addressing batch process challenges: different initial conditions; uneven batch lengths; multiphase feature extraction.	[16•]
Overcomplete broad learning system (OBLS)	FD in a penicillin batch process; a real-world fermenter	Addressing the challenge of non-Gaussian and nonlinearity in data, outperforming traditional PCA and ICA.	[36]
Batch-wise LSTM-AE	FD in a penicillin batch process	Capturing features within and between batches, surpassing AE and Sub-PCA.	[37]
Weak Embryo Detection Network (WEDNet)	FDD of weak and live embryos in egg-based vaccines	Surpassing prior models in processing image time, as well as in the detection and classification of weak embryos.	[38]
Electrical resistance tomography (ERT)	FDD in a reactive crystallization process	Real-time monitoring of $CaCO_3$ reactive crystallization using a single ERT sensor.	[39]
Hybrid model: PLS-EKF	FDD in a penicillin batch process	Improving FDD with augmented datasets of measured and estimated process states.	[40]
Hybrid model: PLS-EKF	FD in a crystallization batch process	PLS-EKF trained with augmented dataset outperforms standard PLS.	[41]
Stochastic hybrid process model (SHPM)	FDD in a penicillin batch process	The proposed SHPM model surpasses Hidden Markov Model (HMM).	[42•]
Ensemble Models: Random Fourier feature analysis (RFFA)	FD in a penicillin batch process	Lower computational load compared with traditional kernel methods, handling large datasets and nonlinear local behaviors.	[43]
Multiway Laplacian autoencoder (MLAE)	FD in a penicillin batch process; a real-world E. coli fermenter	Contrary to traditional AEs, the MLAE model captures both the local structure and deviations among batches.	[44]
Adversarial autoencoder and K-Nearest Neighbor (AAE-KNN)	FD in a penicillin batch process	Outperforms traditional methods such as KPCA and KICA in monitoring minor magnitude and non-Gaussian faults.	[22]
Sequential phase division (SPD)	FD in a penicillin batch process	Monitoring batch multiphase processes with synchronized uneven-length batches.	[45•]
Two-dimensional LSTM variational auto-encoder (2DLSTM-VAE)	FDD in a penicillin batch process	Outperforms complex models like VAE, cVAE, and LSTM-Encoder in addressing nonlinear dynamics and online FDD.	[46]
Siamese deep neighborhood preserving embedding network (SDeNPE)	FD in a penicillin batch process	Outperforming MPCA, NPE, KNPE, SNPE, and DeNPE models despite limited runs and nonlinearity challenges.	[47•]
Multi-way concurrent locally weighted projection regression	FD and QP in a penicillin simulator	Addressing batch process challenges: different operation conditions; multiphase and nonlinearity characteristics.	[48]

Table 1 (*continued*)

Model	Purpose	Results	Ref.
Convolutional block attention module convolutional neural network (CBAM)-CNN	QP in two penicillin fermentation processes	Addressing batch process challenges: different initial conditions; multiphase characteristics; nonlinearity, providing better generalization performance.	[49••]
Multi-stage fusion regression network (MSFRN)	QP in a penicillin batch process	Addressing the oversight of correlations among stages, leading to poor quality prediction in batch processes.	[50]

QP: quality prediction, KPCA: Kernel principal component analysis, KICA: Kernel Independent component analysis.

laws of the process. By partially relying on fundamental governing laws, hybrid models facilitate the estimation of unmeasured process states and enable the augmentation of datasets, thereby enhancing the performance of process monitoring models [25]. For example, physics-informed neural networks (PINN) is a special type of hybrid model that is trained to satisfy the governing physical laws of the process [26].

Fault diagnosis

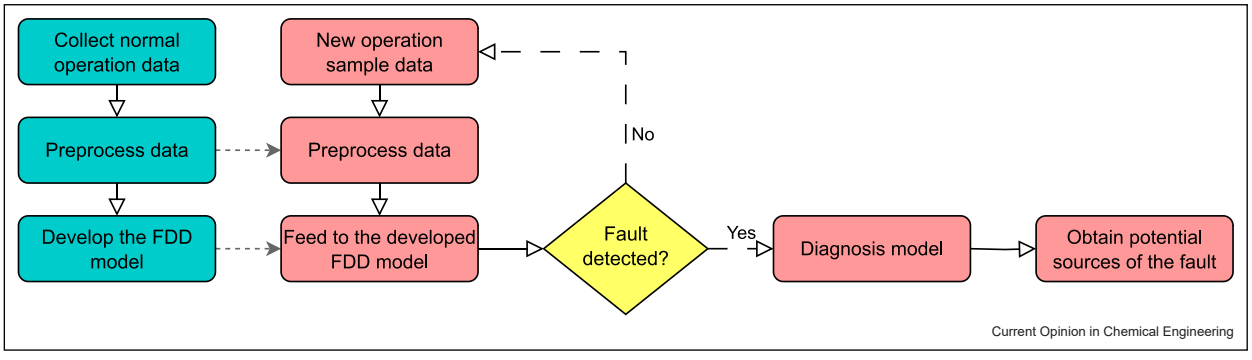
Statistical fault detection charts serve to signal anomalies in a system based on predefined bounds without elucidating the underlying cause. Conversely, fault diagnosis methodologies aim to pinpoint the origin of faults, employing either supervised or unsupervised algorithms. However, supervised approaches necessitate a comprehensive labeled dataset, which is a rarity in practical scenarios. Moreover, information about sources of faults is often scarce in real-world processes. Then, unsupervised algorithms can be used to construct contribution plots that help to interpret and hypothesize potential fault sources. In this regard, two innovative algorithms for generating contribution plots within deep learning process monitoring models have been introduced in Ref. [15••]. Additionally, Artificial Intelligence-based models like AEs in process monitoring tasks can utilize hypothesis testing to assess the differences between the latent space representations of normal and abnormal samples [27,28]. This integration of statistical methods within AI approaches is expected to bolster robustness in model evaluation and validation steps. A summary of recently proposed FDD models for pharmaceutical processes employing machine learning, deep learning, or hybrid approaches is presented in Table 1. Also, Figure 1 presents a flowchart diagram outlining the development of FDD models. The fault detection model is developed using historical batches in offline mode. New samples are labeled as normal or faulty. Faulty samples trigger the diagnosis model to identify the fault source.

For real-time prediction of quality variables and to capture system dynamics within and between batches, especially for dealing with uneven batch lengths, RNN-based models are recommended. CNN-based models are more suitable for capturing multiphase nonlinear processes and offer better generalization performance.

Future prospects

The continuous increase in the elderly population has resulted in a dramatic increase in the demand for pharmaceuticals to address chronic conditions. Also, increased travel and urbanization have raised the risk of spread of infectious diseases, motivating the need for fast manufacturing of vaccines as demonstrated by the recent COVID pandemic [51]. Smart systems that can detect and diagnose faults are crucial for improving the productivity of pharmaceuticals to address this increasing demand at reasonable costs for the public. To

Figure 1



The flowchart of online FDD procedure.

effectively address the aforementioned FDD technical challenges, continuous improvements of existing algorithms are needed. Five main areas for further research are identified as follows:

i. Hybrid models: because of the limited generalization ability of machine learning and neural network models, priority should be given to the advancement of hybrid models as a means of enhancing predictability for input values not used in training. For example, hybrid models could integrate insights from the metabolic network graph, *a priori* knowledge about standard controllers, and physical/biological process constraints.
ii. Definition of normal operation for unsupervised models: process monitoring with unsupervised algorithms relies on data from normal batches for development. However, there is a lack of comprehensive work to label historical batches as either normal or abnormal in a statistically significant manner.
iii. Addressing scarcity of training data: further development is needed on the creation of realistic synthetic data using GANs. Deep learning models often require a substantial amount of training data due to their numerous parameters. GANs offer a promising solution by generating synthetic data that closely mimics real-world scenarios, thereby reducing the reliance on extensive and costly experiments. In the context of pharmaceutical batch processes, GAN models for generating multivariate time series datasets are particularly recommended.
iv. Interpretability of results: because of the complex connectivity of AI models, it is difficult to interpret results. Contribution plots extracted from hybrid models or PINNs could be used for better interpretability.
v. Addressing the issue of uneven batch lengths using dynamic time warping [52] or the indicator variable approach, as utilized in our recent paper [15••].

While research on AI is currently very active, pharmaceutical companies have been slow to adopt artificial intelligence algorithms for online monitoring, despite utilizing them for drug discovery [53] due to challenges such as regulatory hurdles, lack of public trust, data privacy and security concerns, high costs and resource requirements, and cultural resistance to change [54].

Conclusion

The interest in chemical process FDD methods has grown considerably within academia and industry. Despite the concept being introduced approximately 40 years ago, achieving wide industrial acceptance remains a challenge due to trade-offs between technical and regulatory challenges versus resulting profit. In this review, we identified five primary challenges hindering the implementation of smart FDD in biomanufacturing: i) the scarcity of productivity measurements needed for labeling batches as normal or abnormal, impeding supervised learning process monitoring in industry; ii) inadequate information faults occurring in bioprocesses; iii) insufficient data for training DNNs; iv) the interpretability of FDD models to identify fault sources; and v) uneven batch lengths. Unsupervised methodologies are identified as necessary in the absence of labeled batches and prior knowledge of faults. Future prospects for smart process FDD remain expansive and promising, but a clear/ determination of cost versus profit should be established to ensure adoption by practitioners.

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Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

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