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Evolution of chromatographic modeling: From mechanistic models to hybrid models with physics-based deep learning

Yu-Cheng Chen [a,d,e], Zhiyuan Chen [b], Shi-Peng Dai [a,d,e], Youping Xie [a,d,e], Shan-Jing Yao [c], Dong-Qiang Lin [c,*]

[a] *Marine Biological Manufacturing Center of Fuzhou Institute of Oceanography, Fuzhou University, Fuzhou, 350108, China*
[b] *Maynooth International Engineering College, Fuzhou University, Fuzhou, 350108, China*
[c] *Key Laboratory of Biomass Chemical Engineering of Ministry of Education, Zhejiang Key Laboratory of Smart Biomaterials, College of Chemical and Biological Engineering, Zhejiang University, Hangzhou 310058, China*
[d] *Fujian Engineering and Technology Research Center for Comprehensive Utilization of Marine Products Waste, Fuzhou University, Fuzhou, 350108, China*
[e] *Fuzhou Industrial Technology Innovation Center for High Value Utilization of Marine Products, Fuzhou University, Fuzhou, 350108, China*

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ABSTRACT

Hybrid modeling based on physics-based deep learning (PBDL) represents a transformative approach that unifies mechanistic understanding and data-driven learning, offering a pathway beyond the limitations of traditional chromatographic models. This review systematically summarizes the evolution of PBDL methods for chromatography across three generations. The first generation, surrogate-model-based solvers, accelerates simulations through mechanistic up-sampling and fast inference but remains constrained by indirect physical coupling, reflecting “data-assisted physics”. The second generation, physics-informed neural networks, embeds governing equations into the loss function, enabling simultaneous learning from physics and data, while facing challenges in loss balancing and numerical integration, representing “physics-constrained data”. The third generation, differentiable numerical simulations of physical systems, integrates neural networks within numerical solvers, achieving high-fidelity modeling and gradient-based optimization, achieving “mutual feedback between physics and data”. Collectively, these advances empower chromatographic models with the ability to self-learn complex adsorption behaviors under physical constraints, paving the way toward real-time digital twins and intelligent bioprocess modeling for the next generation of chromatographic engineering.

1. Introduction

Traditional chromatographic models are derived from first principles and are commonly referred to as mechanistic models. Over the past two decades, the application of mechanistic models in chromatography has expanded rapidly, encompassing process development and optimization [1,2], process characterization [3,4], real-time process control [5,6], and material traceability [7,8]. These applications have introduced increasingly complex process factors, which in turn pose significant challenges to the development of conventional mechanistic models.

On the one hand, some of these complexities can be addressed by incorporating mechanistic correction terms into the partial differential equations (PDEs) of chromatographic models [9–11], such as those accounting for the influence of salt concentration [12], pH [13], temperature [14], or pore structures [15]. While such modifications can improve model performance, they also introduce many new model parameters [16,17], thereby increasing model dimensionality and complexity. As a result, more experimental data and more efficient parameter estimation methods are required [18–20], and the associated computational costs and runtimes increase considerably, reducing the timeliness of model-assisted process development in the early stages. For example, extending the standard steric mass action (SMA) model to account for pH effects requires constructing independent SMA models at each pH condition [17]. If three gradient elution experiments are needed for each SMA model, the full pH model would require nine experiments. Thus, extracting physically meaningful parameters from minimal experimental data remains a key challenge in chromatographic modeling.

The interplay among the number of model parameters, the size of the training dataset, and computational resources generally follows a

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* Corresponding author.
E-mail address: lindq@zju.edu.cn (D.-Q. Lin).

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predictable scaling law [21] as shown in Fig. 1: model performance tends to improve according to a power-law relationship with the growth of a single factor. However, there is growing concern that scaling laws may eventually fail, i.e., model performance may plateau beyond a certain parameter scale, such that further parameter expansion yields diminishing returns.

On the other hand, some chromatographic behaviors, such as complex nonlinear adsorption [22], nonideal effects [23], and structure-property relationships [24–27], cannot be readily explained by existing mechanistic knowledge and therefore require data-driven corrections to fully mechanistic models. Early hybrid approaches are often coupled mechanistic models with linear or polynomial regressions [28]. While such strategies provided a pragmatic means to describe unidentifiable behaviors, they were largely intuitive and lacked a systematic framework for hybrid modeling.

A comprehensive hybrid modeling framework should follow a unified development paradigm, retaining the advantages of both fully mechanistic and fully data-driven models while mitigating their limitations [29–35]. Mechanistic models provide physical interpretability and small-sample learning, whereas data-driven models contribute strong learning capacity and rapid inference [36]. However, the lack of seamless integration between these two paradigms often limits their combined potential in practical chromatographic modeling. Deep learning, with its remarkable expressiveness and flexibility, offers a natural bridge between mechanistic principles and data-driven knowledge. Building on this synergy, the resulting hybridized approach, often referred to as physics-based deep learning (PBDL) [37], integrates physical modeling and numerical simulations with deep learning techniques to improve the fidelity, efficiency, or interpretability of fully mechanistic models. PBDL thus holds the potential to surpass fully mechanistic modeling and emerge as the next generation of chromatography models.

In this review, we summarize the development of PBDL approaches for chromatographic modeling. The evolution of these methods can be broadly categorized into three generations, based on how mechanistic knowledge and data-driven learning are integrated as shown in Fig. 2. The first generation, surrogate-model-based solvers, accelerates simulations through mechanistic up-sampling and fast inference but remains constrained by indirect physical coupling, reflecting “data-assisted physics”. The second generation, physics-informed neural networks (PINNs), embeds governing equations into the loss function, enabling simultaneous learning from physics and data, while facing challenges in loss balancing and numerical integration, representing “physics-constrained data”. The third generation, differentiable numerical simulations of physical systems, also known as differentiable physics (DP), integrates neural networks within numerical solvers, achieving high-fidelity modeling and gradient-based optimization, achieving “mutual feedback between physics and data”. In the following sections, we systematically review these three generations, highlighting their methodologies, advantages, limitations, and applications in chromatographic modeling.

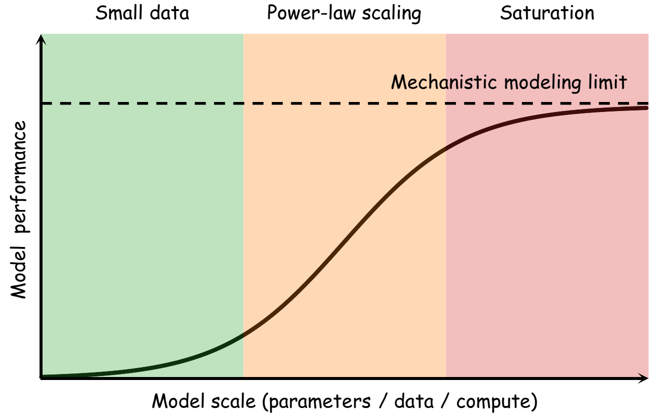

Fig. 1. Model performance scaling across small-scale, power-law, and saturation regimes approaching the mechanistic limit.

2. Surrogate solvers

Surrogate solvers represent the natural starting point of PBDL [37]. Their essence lies in replacing complex and computationally expensive PDE solvers with fast, learned approximations using surrogate models, thereby reducing the computational burden of numerical methods and improving the efficiency of chromatographic modeling.

Conceptually, the overall workflow of surrogate solvers involves two main components—a mechanistic PDE solver and a surrogate model trained to approximate it. As summarized by Nagrath et al. [38], the development of surrogate solvers typically proceeds through three steps: (1) calibration of the mechanistic chromatographic model using a limited set of experimental data; (2) sampling across the process parameter space to generate large amounts of synthetic data from the calibrated model; and (3) training the surrogate model with process parameters and their corresponding numerical solutions as reliable input-output pairs. This workflow, illustrating the hybrid coupling between mechanistic and data-driven models, is schematically depicted in Fig. 2B Such a hybrid training strategy enables surrogate solvers to inherit both the strengths and limitations of fully mechanistic and fully data-driven approaches.

In practice, surrogate models are often implemented as fully connected neural networks composed of an input layer, multiple hidden layers, and an output layer, as schematically illustrated in Fig. 2A. These networks are trained to learn the mapping between critical process parameters (CPPs) and chromatograms, serving as efficient functional approximations of mechanistic PDE solvers.

In addition, other machine learning models such as Gaussian process regression (GPR) can also be employed as surrogate models [39–42]. As compared in Fig. 3, the key difference lies in the target of learning. Neural networks generally capture the mapping between CPPs and complete chromatograms, providing a versatile framework in which any critical quality attribute (CQA) of interest can subsequently be extracted. This paradigm may be referred to as chromatogram-based learning. In contrast, GPR is typically trained to map CPPs directly to specific CQAs, providing a more targeted approach known as CQA-based learning. However, when the set of interest CQAs changes, the GPR model must be retrained accordingly. It is worth noting that the amount of data required to train a GPR model for CQAs is generally smaller than that needed for chromatogram-based learning. Since GPR does not involve deep learning architectures, the CQA-based learning is generally classified as physics-based machine learning rather than PBDL.

2.1. Advantages of surrogate solvers

2.1.1. Small-sample learning through mechanistic up-sampling

Compared with fully data-driven models, surrogate solvers employ mechanistic simulations as a form of up-sampling. This small-sample strategy alleviates the common limitation of insufficient experimental datasets in chromatographic modeling. For instance, Pirrung et al. [43] combined the Mollerup thermodynamic model (which accounts for ion-exchange, hydrophobic interaction, and mixed-mode chromatography) with artificial neural networks to construct a surrogate solver. When trained on the same dataset, the predictions were nearly indistinguishable from those of the fully mechanistic model, demonstrating that surrogate solvers retain the advantage of small-sample learning inherent to mechanistic approaches.

2.1.2. Fast inference through mechanistic guidance

The design of surrogate solvers is tailored according to chromatographic process knowledge and application needs. Inputs generally

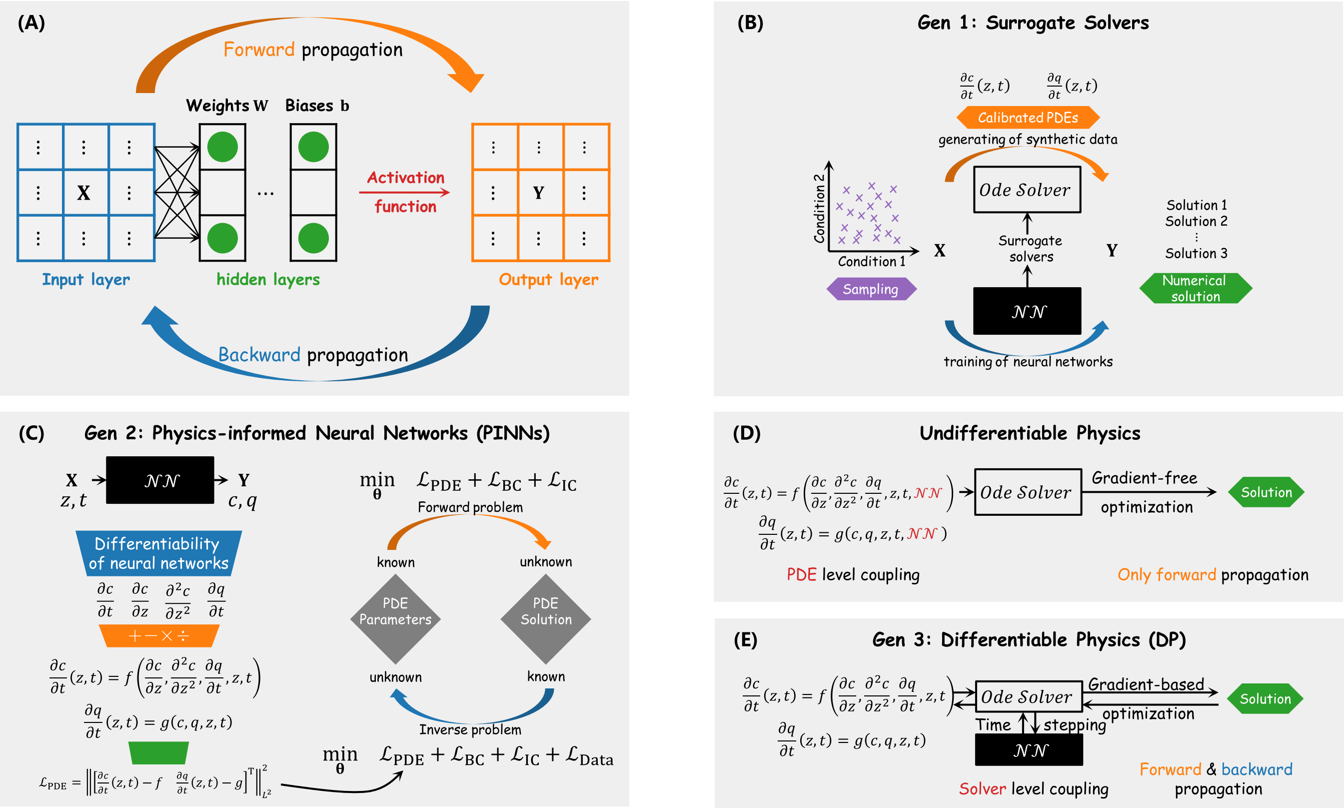

Fig. 2. (A) Architecture of a fully connected neural network. (B) PBDL Gen 1, surrogate solvers: mechanistic up-sampling and fast inference, "data-assisted physics". (C) PBDL Gen 2, PINNs: governing-equation-embedded loss functions, "physics-constrained data". (D) undifferentiable numerical simulations: neural-network integration at the model level without differentiability or backpropagation. (E) PBDL Gen 3, DP: neural-network-enhanced numerical solvers at the solver level, "mutual feedback between physics and data".

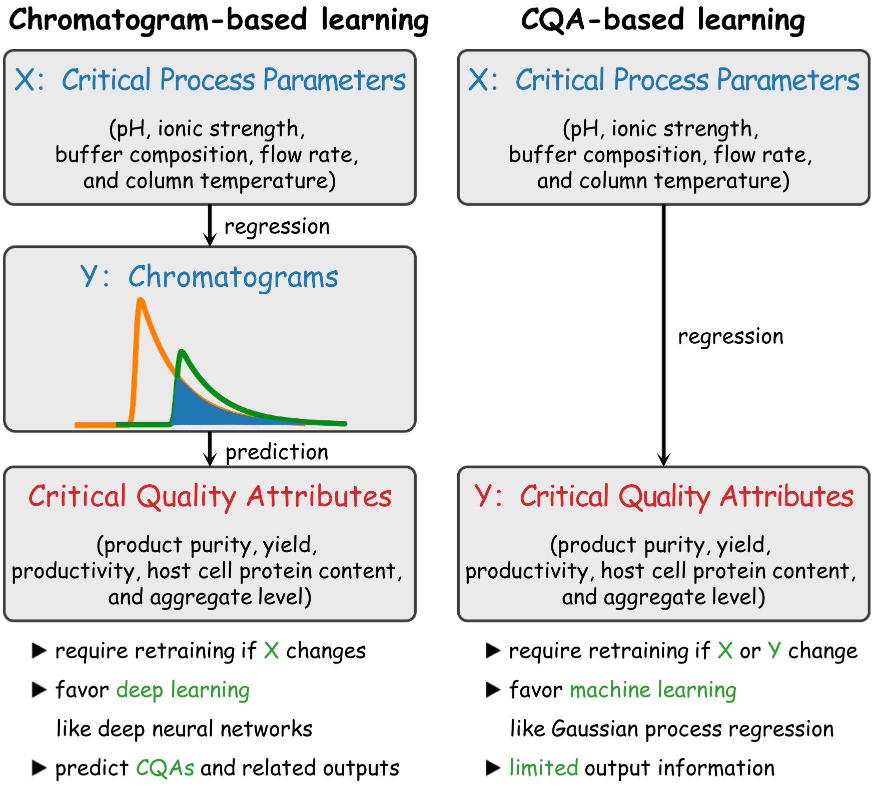

Fig. 3. Comparison of chromatogram-based learning (typically using deep learning) versus CQA-focused learning (typically using machine learning).

consist of process parameters with a pronounced impact on chromatographic performance, while outputs are typically restricted to outlet concentrations, eliminating the need for spatial discretization. Unlike fully mechanistic models, which must compute internal concentration profiles along the column, surrogate solvers can directly predict outlet concentrations for specific chromatographic phases (e.g., the elution step) without simulating preceding stages such as loading or washing.

By bypassing time integration and spatial discretization, surrogate solvers achieve rapid and fixed-time inference, making them particularly attractive for computation-sensitive applications such as real-time process optimization. Nagrath et al. [38] demonstrated that surrogate solvers significantly reduced simulation and optimization runtimes for ion-exchange chromatography. Furthermore, Pirrung et al. [43] quantified over 50 % acceleration of surrogate solvers relative to fully mechanistic chromatographic models. For optimization of continuous processes such as multi-column counter-current solvent gradient purification (MCSGP), the computational speedup using surrogate solvers reached as high as 97 % compared to mechanistic model-based optimization [44]. These results highlight the great promise of surrogate solvers for computation-intensive applications, particularly in continuous chromatography, which is expected to play a central role in future technological advances.

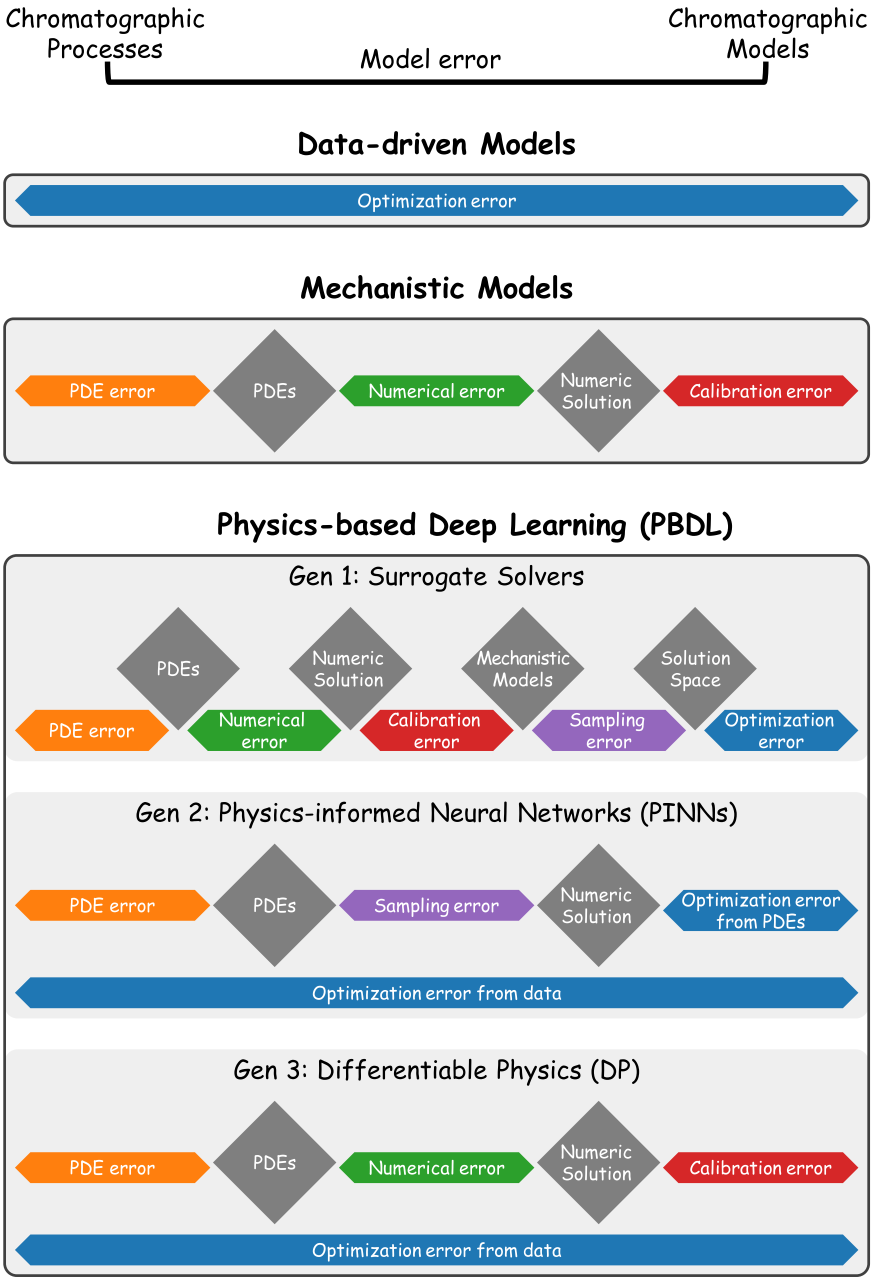

Fig. 4. Representative types of errors between real-world chromatographic processes and their corresponding models, including PDE error (orange), numerical error (green), calibration error (red), sampling error (purple) and optimization error (blue). Their relative contributions vary across the three generations of PBDL methods: surrogate models (Gen 1) are dominated by PDE, numerical, and calibration errors; PINNs (Gen 2) primarily exhibit sampling and optimization errors; and DP methods (Gen 3) mainly feature numerical and optimization errors. Notably, both Gen 2 and Gen 3 possess data-driven optimization pathways that can partially counterbalance other error sources, enabling improved overall accuracy.

2.2. Limitations of surrogate solvers

2.2.1. Constrained by PDE error and indirect learning

Surrogate solvers approximate PDE solvers, and their performance therefore depends critically on the quality of the governing PDEs used to generate synthetic data. As with all data-driven methods, the “garbage-in-garbage-out” principle applies [45]: the PDEs must be sufficiently expressive to describe real-world chromatographic behavior. Yet, because most chromatographic PDEs are derived under simplifying assumptions, discrepancies between simulations and reality are inevitable, which is denoted as PDE error (Fig. 4). Moreover, since surrogate solvers inherit their training data entirely from fully mechanistic models, they are inherently limited to reproducing phenomena already captured within the mechanistic framework and cannot uncover new physical insights directly from experimental data.

2.2.2. Constrained by numerical error, data cost, and accuracy limits

In addition to model assumptions, surrogate solvers inherit numerical error from the discretization schemes used in mechanistic simulations. Michalopoulou and Papathanasiou [46] emphasized that high-fidelity numerical solvers are essential for ensuring the reliability of surrogate approaches. Consequently, surrogate solvers are most suitable for applications where strict accuracy is not critical, such as the global search phase of chromatographic process optimization [43]. Furthermore, generating hundreds or thousands of mechanistic solutions to populate the training space can be computationally expensive, and efficiency depends strongly on solver performance and parallelization strategies [38].

Given these challenges, the accuracy of surrogate solvers can never exceed that of the underlying mechanistic model, as shown in Fig. 4. This limitation underscores the need for modeling strategies that go beyond calibrated mechanistic frameworks and can directly learn from experimental data while preserving physical consistency.

3. Physics-informed neural networks

PINNs represent the second generation of PBDL approaches, first introduced by Raissi et al. [47–49] around 2017. Unlike surrogate solvers, which depend entirely on mechanistic simulations for training data, PINNs integrate the governing physical laws directly into the neural network learning process. This hybrid model is achieved through a composite loss function that simultaneously includes three terms [50]: the PDE loss, which enforces the governing equations of chromatographic mass transport and adsorption; the boundary and initial condition losses, which ensure compliance with system constraints; and the data loss, which aligns model predictions with experimental observations.

As presented in Fig. 2C, the PDE loss and boundary/initial condition losses are evaluated by exploiting the differentiable nature of neural networks [51]. A typical PDE governing chromatographic processes consists of multiple differential terms—such as spatial and temporal gradients—that describe the rates of mass transport and adsorption. In PINNs, the neural network takes spatial and temporal coordinates as inputs and outputs the corresponding transport and adsorption states. Through automatic differentiation, the gradients of these outputs with respect to time and space can be computed efficiently and exactly, eliminating the need for traditional numerical approximation schemes [52]. This mechanism allows PINNs to directly embed the governing physics into the optimization process, ensuring that the predicted solutions inherently satisfy both the physical equations and the associated boundary and initial conditions [53].

Beyond physical constraints, the data loss can introduce data-driven adaptability into the model. It is typically formulated as the mean squared error between network predictions and experimental data points [54–56], enabling the network to learn from empirical observations. This term allows PINNs to compensate for modeling inaccuracies arising from imperfect PDE assumptions or uncertain parameters, thereby enhancing predictive accuracy and robustness in real-world chromatographic systems beyond the limits of mechanistic frameworks.

By unifying physics-based formulation and data-driven learning within a single framework, PINNs offer a balanced paradigm that preserves the interpretability and physical consistency of PDE-based models while harnessing the flexibility and generalization power of deep learning. This synergy represents a major step forward in the evolution of PBDL for chromatography, laying the foundation for more accurate, efficient, and physically grounded modeling of complex chromatographic processes.

3.1. Advantages of physics-informed neural networks

*3.1.1. **Learning** unknown mechanisms through **data loss***

In contrast to surrogate solvers or fully mechanistic models, which often require explicit modifications of the governing PDEs to account for unidentifiable behaviors, PINNs can capture complex chromatographic phenomena directly through the data loss. In practical applications, this capability has been demonstrated in several studies. Subraveti et al. [57–59] applied PINNs to adsorption models in chromatography, showing that the network could learn unidentifiable adsorption mechanisms from experimental data, maintaining norm errors between model predictions and experiments below 1 %. Similarly, Santana et al. [60] employed PINNs to model ion-exchange chromatography for monoclonal antibodies and achieved an exceptionally low prediction error of 0.1 % relative to experimental measurements.

Furthermore, Fig. 4 illustrates representative types of errors in real-world chromatographic processes compared to their corresponding models. For surrogate solvers or fully mechanistic models, errors such as PDE error, numerical error, calibration error, sampling error, and optimization error are generally unavoidable. In contrast, PINNs do not require discretization or external solvers, eliminating numerical and calibration errors and providing higher intrinsic accuracy. More importantly, the optimization error in PINNs has two complementary pathways: one arising from the PDE residual and the other from the data loss. These two contributions can compensate for each other, and under ideal conditions, they may fully offset, enabling highly precise process modeling.

These results demonstrate that, by learning from experimental data while respecting physical laws, PINNs can capture subtle chromatographic phenomena beyond the reach of fully mechanistic models, enabling more accurate and insightful process predictions.

3.1.2. Fast inference through pre-trained PINNs

Pre-trained PINNs can function solely as PDE solvers in the absence of experimental data, efficiently addressing forward problems [61], where system behavior is predicted from known PDEs and model parameters, as shown in Fig. 2C. During pre-training, the neural network is exposed to a wide range of PDE scenarios by sampling model parameters within specified bounds and learning from multiple PDE instances rather than a single equation. This process allows the network to capture the general behavior of the system across different conditions. This pre-trained model can be directly used for rapid inference under new parameter sets or operating conditions, evaluating how well the PDEs are satisfied without retraining.

For instance, Söderström [62] applied PINNs to solve linear adsorption models and reported a 23-fold speedup over classical numerical solvers, while Tang et al. [63] demonstrated that combining lumped kinetic and Langmuir models could be solved in only 30 s compared to 7–72 min with traditional numerical methods.

These results highlight that pre-trained PINNs provide rapid inference while rigorously embedding physical constraints, making them highly suitable for computationally intensive or time-sensitive chromatographic applications.

3.1.3. *Parameter estimation through inverse problem solving*

Another advantage of PINNs lies in their capability to estimate unknown PDE parameters through inverse problem solving [64,65]. As shown in Fig. 2C, an inverse problem refers to inferring hidden system properties, such as mass transfer and adsorption parameters, from observed experimental data. The unknown PDE parameters are incorporated as trainable variables together with the neural network's weights and biases. Through automatic differentiation, the network efficiently computes gradients of both state variables and mechanistic parameters with respect to spatial and temporal inputs, thereby enabling the optimization of PDE parameters.

Zou et al. [66] employed PINNs to fit mass transfer and adsorption coefficients in chromatographic models using chromatograms as fitting targets, achieving up to a 95 % reduction in computation time and a 35 % decrease in fitting error across diverse experimental conditions. Tang et al. [67] applied PINNs to model monoclonal antibodies in periodic counter-current chromatography, reducing breakthrough curve fitting time from 2608.6 s with numerical solvers to 110.7 s, while facilitating online optimization of yield and resin utilization. In contrast to these chromatogram-based fitting approaches, Punj et al. [68] used PINNs to fit the relationship between normalized gradient slope and ionic strength at the retention time. Since this method does not involve PDEs, it achieved an R^2 of 0.999 in just 90 s. This approach has subsequently been applied in their follow-up studies for separation of Fab therapeutic charge variants by ion-exchange chromatography [69].

Collectively, these studies highlight that PINNs provide a efficient framework for solving inverse problems in chromatography, achieving both rapid convergence and high parameter accuracy, marking a advance in the evolution of PBDL modeling.

3.2. *Limitations of physics-informed neural networks*

3.2.1. *Constrained by loss-weight imbalance and limited physical enforcement*

Despite the advantages of PINNs in integrating physical laws with data-driven flexibility, their performance in chromatographic modeling is constrained by challenges in designing loss function weights. The composite loss typically comprises PDE residual loss, boundary/initial-condition losses (collectively, physical losses), and data loss. Physical losses often differ markedly in scale, units, and gradient sensitivity, making naive weighting prone to imbalance. This can destabilize training, weaken enforcement of boundary/initial conditions, and increase overfitting risk. Specifically, Santana et al. [60] highlighted that weight design directly affects predictive accuracy; Söderström [62] emphasized its importance for matching boundary conditions; Tang et al. [63] showed that equal weighting causes convergence difficulties; Zou et al. [66] reported that poorly chosen weights could degrade training efficiency and final performance; Subraveti et al. [58,59] provided theoretical evidence that weight imbalance could increase overfitting risk and highlighted the need for a generalizable strategy to select weights.

Traditionally, the design of loss function weights has relied heavily on empirical choices or trial-and-error. For example, Santana et al. [60] adaptively adjusted the inlet-boundary weight from 1×10^{-4} to 1 while fixing all other weights at 1. Tang et al. [63] arbitrarily set the column inlet weight to 0.1 without further justification. In preparative chromatography applications, Subraveti et al. [58] and Zou et al. [66] adopted the same strategy by assigning identical weights to the four physical losses and testing only three physical-to-data weight ratios (1:1, 1:10, 1:100). The best-performing ratio (1:100) occurred at the edge of the search space, indicating limited methodological basis. Similarly, Subraveti et al. [59], when studying binary separation systems, again fixed all physical loss weights identically while arbitrarily assigning the data loss weights of 2 and 1.5 to components 1 and 2, respectively. Overall, existing weighting practices lack a principled foundation, and the number of required weights scales rapidly with system dimensionality. Such combinatorial growth makes fully empirical tuning inefficient and impractical.

To address this, Chen et al. [70] proposed a systematic weighting strategy based on the order-of-magnitude analysis, a classical tool in chemical engineering for assessing the relative significance of physical quantities. They estimate the characteristic magnitude of each PDE term of linear chromatographic models and assign its reciprocal as the weight for the corresponding physical losses. This physically grounded scheme balances PDE and boundary/initial-condition losses, reduces hyperparameter tuning, improves convergence, and mitigates overfitting. The validation results showed three to four orders of magnitude gains in accuracy, 32 × reduction in required grid density, higher convergence order, and up to 1000 × speedup relative to standard PINNs and discontinuous Galerkin finite element method.

An alternative approach is to reduce the reliance on soft loss balancing altogether by enforcing physical constraints more strictly [71]. Standard PINNs impose PDEs and boundary/initial conditions as soft constraints in the loss [72,73]. By contrast, hard-constraint techniques embed certain boundary/initial conditions or conservation laws directly into the network architecture or output mapping so that they are satisfied exactly by construction [61]. This reduces sensitivity to loss-term weighting and enhances extrapolation performance.

In short, the primary limitation of PINNs is balancing PDE loss versus boundary/initial condition losses. Remedies focus on physically informed weighting and hard-constraint enforcement, which can be combined for improved reliability in future chromatographic applications.

3.2.2. *Constrained by limited compatibility with classical numerical methods*

Another notable limitation of PINNs lies in their limited compatibility with classical numerical methods. Unlike finite element or finite difference methods, PINNs construct solutions independently through neural network representations, relying on soft physical constraints to encode PDEs [74,75]. Thuerey et al. [37] highlighted that this computational paradigm differs substantially from established numerical techniques, preventing decades of accumulated numerical expertise and optimization strategies from being directly applied. Consequently, many powerful methods developed over the past decades for improving accuracy, stability, and efficiency in chromatographic PDE simulations cannot be readily leveraged within the PINNs framework [76–80]. Overcoming this incompatibility and integrating the strengths of traditional numerical methods into PINNs remains an important challenge for future research.

4. Differentiable physics

The evolution from surrogate solvers to PINNs has progressively strengthened the integration of physical modeling with deep learning. However, as mentioned above, a major limitation of PINNs is their poor compatibility with classical numerical methods, preventing the reuse of decades of accumulated numerical expertise. To address this, a new paradigm—differentiable numerical simulations of physical systems (DP)—has emerged, enabling a deeper integration of deep learning and numerical simulation. As suggested by Thuerey et al. [37], DP represents the ultimate evolutionary stage of PBDL, combining the differentiability of neural networks with the rigor and efficiency of established numerical solvers.

4.1. *Undifferentiable physics: constrained by the lack of gradient-based optimization*

Before the emergence of DP, early PBDL methods adopted undifferentiable physics (Fig. 2D), which differ from both surrogate solvers and PINNs in their approach to integrating mechanistic knowledge with neural networks. Unlike surrogate solvers, which replace or approximate the entire PDE solver with a learned model, undifferentiable physics retains the full mechanistic PDEs and introduces neural networks rather than new model parameters only at the model level, as additive correction terms to account for discrepancies between experimental data and mechanistic predictions. In contrast to PINNs, which embed PDEs directly into the loss function for end-to-end gradient-based learning, undifferentiable physics does not allow for gradient-based optimization across the entire simulation workflow.

In chromatographic modeling, undifferentiable physics used neural networks to capture complex adsorption dynamics while retaining first-principle PDEs for column transport, achieving notable success in describing capture [81], hydrophobic interaction [82], and reactive chromatography [83].

However, undifferentiable physics has two fundamental limitations. First, because the neural networks are integrated at the model level, its predictive performance heavily depends on the empirical integration of neural and mechanistic components, without a unified framework. For instance, different mass-transfer or adsorption terms may be represented by neural networks or PDEs, requiring extensive empirical consideration [81,82]. Frandsen et al. [83] systematically explored ten possible integration strategies using the Langmuir model as a baseline, greatly increasing workload. For more complex adsorption models, the number of potential integration schemes could grow exponentially, making brute-force enumeration infeasible.

Second, training relies on least-squares optimization rather than gradient-based learning, ignoring differentiability and backpropagation [84,85]. This restricts models to shallow neural networks. As network depth or system complexity increases, convergence becomes unstable and local minima are more likely. These constraints limit scalability and learning efficiency of undifferentiable physics, motivating the need for DP to enable gradient-based optimization within numerical solvers.

4.2. *Differentiable physics: integrating deep learning and numerical solvers*

DP addresses the limitations of undifferentiable physics by integrating neural networks directly at the solver level [86]. Fig. 2 clearly illustrate the distinction between undifferentiable physics (Fig. 2D), where neural networks are incorporated at the model level, and DP (Fig. 2E), which embeds networks within the numerical solver itself, enabling bidirectional gradient flow between neural network components and the physical simulation. As implemented in the DP, existing numerical solvers are augmented to compute gradients of outputs with respect to inputs and parameters. Once all computational operators are differentiable, automatic differentiation and backpropagation can be applied throughout the simulation, enabling efficient gradient-based optimization of both physical parameters and network weights.

A common implementation is the DP solver-in-the-loop approach [87], where differentiability and backpropagation are incorporated within the solver's time-stepping procedure. The DP solver allows gradient flow between the solver and neural networks, reducing numerical errors while retaining the rigor of conventional solvers. This framework effectively bridges numerical solvers and deep learning, combining established numerical knowledge with optimization capabilities of modern neural architectures.

4.3. *Advantages of differentiable physics*

4.3.1. *High-fidelity modeling through solver-level integration*

One major advantage of DP lies in its ability to achieve highly accurate modeling of complex chromatographic processes. Um et al. [87] demonstrated that applying DP to convection-dispersion equations improved accuracy by approximately 40 % over conventional numerical solvers. Similarly, when applied to fluid dynamics problems such as the Navier-Stokes equations [88], DP solvers have shown strong generalization performance across diverse flow conditions.

For chromatography, DP hybrid models can integrate mechanistic understanding with neural network learning to capture behaviors that fully mechanistic models alone cannot describe. For example, Chen et al. [22] developed a DP hybrid model for oligonucleotide reversed-phase chromatography, successfully representing a strongly adsorbed impurity exhibiting a transition from anti-Langmuirian to Langmuirian adsorption—a phenomenon that has recently attracted considerable attention in adsorption field [16,17,89–100]. The DP hybrid model reduced overall prediction error to less than one-tenth of the fully mechanistic model, demonstrating superior fidelity in capturing complex adsorption phenomena.

4.3.2. *Strong extrapolability through mechanistic guidance*

Another essential advantage of DP hybrid models is their ability to achieve strong extrapolative predictions even when trained on limited experimental data. Fully data-driven models typically interpolate within the training range, whereas DP hybrid models leverage mechanistic knowledge, including governing PDEs describing mass transport and intra-particle diffusion, adsorption isotherm models capturing equilibrium binding, to extrapolate to unseen conditions.

In bioprocessing, obtaining sufficient high-quality experimental data is often challenging [26,101–103], making small-sample learning highly desirable [104,105]. Ideally, hybrid models should require data comparable to fully mechanistic models, enabling a seamless transition and performance comparisons without additional experiments.

For instance, in oligonucleotide reversed-phase chromatography, Chen et al. [22] constructed a DP hybrid model by embedding mechanistic chromatographic equations directly into a differentiable physics solver. The mechanistic backbone consisted of the equilibrium dispersive model describing axial transport and dispersion inside the column, coupled with a stoichiometric displacement model to represent adsorption thermodynamics. Within this framework, a neural network was introduced to learn the nonlinear influence of organic solvent fraction on the adsorption process, while all transport dynamics governed by the equilibrium dispersive model remained explicitly enforced through DP operators. This integration occurs at the solver level: during training, the neural network outputs are propagated through the discretized mechanistic equations, and gradients are computed via automatic differentiation. As a result, the learned corrections remain physically consistent, and the model predictions satisfy the governing PDEs and adsorption constraints by construction. Using only three linear gradient elution experiments for training, the DP hybrid model accurately predicted chromatographic outcomes for previously unseen gradient slopes and loading conditions, with independent test experiments confirming robust extrapolative performance. The strong external validity arises from combining mechanistic fidelity with data-driven flexibility through the neural network, enabling reliable predictions under data-limited conditions typical of high-cost biopharmaceutical processes.

4.3.3. *Efficient gradient-based training through network differentiability*

DP hybrid models also enable gradient-based optimization by exploiting the differentiable nature of neural networks. Traditional least-squares training ignores gradient information and is effective only for shallow networks [81,82]. In contrast, DP solvers compute gradients of outputs with respect to inputs and parameters, supporting deep networks and high-dimensional parameter spaces. This capability ensures robust convergence, efficient training, and scalability to complex chromatographic systems.

Overall, DP hybrid models effectively integrate mechanistic modeling and deep learning. The relative contribution of the mechanistic and data-driven components can be quantified by the hybridization degree proposed by Narayanan et al. [85]. In the DP hybrid model, the hybridization degree is approximately 0.6 % [22], indicating predominant reliance on mechanistic components. This explains the

Table 1
Comparison of the key features of fully data-driven, fully mechanistic, and three generations of PBDL hybrid chromatographic modeling approaches.

Modeling method	Unknown mechanism description	Small-sample learning	Fast inference	Modeling accuracy	Extrapolative prediction	Compatibility with numerical methods	No loss-weight design
Fully data-driven method	✓		✓	✓			
Fully mechanistic model		✓			✓	✓	✓
Surrogate sovlers		✓	✓			✓	
PINNs	✓	✓	✓	✓			
DP	✓	✓		✓	✓	✓	✓

retention of mechanistic features such as small-sample learning and strong extrapolability under limited data conditions. Compared with PINNs, DP models maintain compatibility with classical numerical solvers, leveraging decades of numerical expertise. Compared with undifferentiable physics approaches, DP eliminates manual neural network-PDE coupling and exploits backpropagation and differentiability of neural networks, enabling efficient gradient-based optimization and deeper network architectures. These advantages establish DP as an evolutionary advancement in PBDL for chromatography modeling, combining physical fidelity, computational efficiency, and learning capability.

4.4. *Limitations of differentiable physics*

Despite the promising advantages, DP hybrid models still face several limitations. First, implementing DP solvers is technically demanding, as they require the simultaneous integration of mechanistic models and neural networks within a unified differentiable framework. This process involves challenges such as formulating PDEs, performing spatial discretization, time integration, designing neural network architectures, and optimizing hyperparameters. Consequently, developing DP models demands expertise in both numerical analysis and deep learning, posing a steep learning curve for practitioners.

Second, DP solvers still rely on numerical solvers, which increases computational effort. During training, the computational burden of DP hybrid models is typically comparable to the combined burden of mechanistic and data-driven models, since each iteration involves both numerical simulation and neural network backpropagation. Furthermore, DP methods require storing gradient information, leading to substantial memory consumption—especially for large-scale or multi-dimensional chromatographic systems. However, it is important to emphasize that this overhead exists primarily during training; during inference, DP models need not store gradient information, freeing memory resources and improving deployment efficiency. Importantly, DP solvers can leverage GPU-based parallelization to accelerate computations, often outperforming traditional CPU-based numerical methods despite the additional computational complexity. Achieving comparable throughput on GPUs may entail higher hardware costs compared to CPUs, reflecting a shift from computational time expenditure to infrastructure investment.

In summary, while DP hybrid models represent the most advanced form of PBDL by unifying mechanistic modeling and differentiable computation, their high implementation complexity and computational cost still limit their widespread application. Nevertheless, DP marks a crucial milestone in the evolution of hybrid modeling, pushing the boundary from data-assisted physics toward truly differentiable numerical intelligence.

5. Comparative analysis of three generations of hybrid chromatographic modeling

To better contextualize the advantages and limitations of hybrid mechanistic-data modeling, this section presents a comparative analysis of the three generations of hybrid chromatographic modeling approaches—surrogate solvers, PINNs, and DP. A summary of their key characteristics across seven core modeling dimensions is provided in Table 1.

The evolution of these three paradigms reflects a continuous deepening of mechanistic-data integration: from the indirect coupling of surrogate solvers to the loss-based physical embedding of PINNs, and finally to the solver-level differentiability of DP. Each generation exhibits distinct trade-offs in coupling depth, training complexity, inference efficiency, and applicable scenarios, collectively marking the coevolution of physical interpretability and data-driven adaptability in chromatographic modeling.

5.1. Mechanistic-data coupling

The first generation of PBDL, surrogate solvers, achieve indirect mechanistic-data integration by generating synthetic data, limiting coupling to the input-output mapping layer and lacking the ability to extract unknown mechanisms from experimental observations. The second generation of PBDL, PINNs, embed physical equations and experimental data simultaneously through loss function constraints, enabling the model to respect known physical laws while capturing previously unidentified mechanisms via data-driven loss terms. The third generation of PBDL, DP solvers, integrate neural networks directly into the numerical computation core, allowing co-optimization of physical laws and data features at the solver level, representing the deepest mechanistic-data fusion.

5.2. Training cost

Surrogate solvers concentrate computational effort in the initial generation of synthetic datasets, enabling extremely fast inference once training is completed. PINNs, however, require iterative tuning of loss function weights, resulting in longer training times. DP solvers demand simultaneous optimization of neural network parameters and physical equation solutions, yielding the highest training complexity among the three generations.

5.3. Inference speed

Surrogate solvers can decouple entirely from numerical solvers during inference, achieving significant speedups. PINNs exploit mesh-free evaluation for rapid predictions. DP solvers can leverage GPU-based parallelization to accelerate computations, often outperforming traditional CPU-based numerical methods despite the additional computational burden.

5.4. Applicable scenarios

The first generation of PBDL, surrogate solvers, are suited for tasks where computational efficiency is paramount. They are particularly useful for rapid exploration of process conditions, preliminary design of continuous chromatography systems [44], or generating large synthetic datasets for mechanistic model training [57–59], albeit with limited accuracy that can be refined subsequently [43].

The second generation of PBDL, PINNs, are appropriate when both fast inference and high fidelity are required. They can be applied to model chromatographic systems with complex adsorption behaviors, capture previously unidentifiable mechanistic effects from experimental data [106], and enable rapid parametric studies [107] or online process monitoring under moderate computational cost [108,109].

The third generation of PBDL, DP solvers, excel in the applications demanding high-accuracy extrapolative predictions, small-sample learning, and gradient-based optimization under complex operating conditions. They are especially promising for constructing real-time digital twins of chromatographic processes with GPU acceleration, predicting system behavior under novel operating conditions, modeling complex adsorption phenomena [22], and optimizing multi-component separation with minimal experimental input.

While these hybrid models demonstrate strong performance in small-scale settings, their applicability to preparative-scale columns warrants further investigation. Large columns introduce scale-dependent factors such as packing heterogeneity, porosity variations, pressure-induced resin compression, and batch-to-batch changes in adsorption behavior, which may alter transport-adsorption interactions in ways not fully captured by small-column training data. Mechanistic chromatographic models provide useful precedents through scale-aware transport correlations and isotherm formulations [16,110,111], suggesting that incorporating similar physical constraints and developing multi-scale benchmark datasets will be important for extending hybrid modeling toward reliable laboratory-to-manufacturing scale transitions.

5.5. Outlook

The technological evolution of hybrid mechanistic-data dual-driven modeling represents a progressive synergy between the depth of physical embedding and the flexibility of data-driven learning. First-generation surrogate solvers increase computational speed by “data-assisted physics”, second-generation PINNs enhance interpretability through “physics-constrained data”, and third-generation DP solvers achieve dynamic co-adaptation via “mutual feedback between physics and data”. As suggested by Thuerey et al. [37], DP represents the ultimate evolutionary stage of PBDL, combining the differentiability of neural networks with the rigor and efficiency of established numerical solvers.

Nevertheless, DP methods still face two notable challenges. First, developing DP hybrid models requires multidisciplinary expertise in PDE formulation, numerical discretization, and deep learning optimization, imposing a steep learning curve for practitioners. This barrier may be alleviated through the emergence of high-level DP libraries, automated solver construction frameworks, and the cultivation of interdisciplinary talent trained at the interface of computational science and biochemical engineering. Second, DP solvers typically rely on GPU-based parallelization, incurring substantial memory consumption and hardware investment costs. Ongoing advances in numerical algorithms, differentiable programming frameworks, memory-efficient back-propagation strategies, and distributed heterogeneous computing are expected to mitigate these constraints and further broaden the accessibility of DP-based chromatographic modeling.

Looking ahead, the continued maturation of PBDL promises to drive chromatographic engineering toward real-time, adaptive, and prediction-driven operation. By bridging the limitations of fully mechanistic or fully data-driven modeling, hybrid approaches support more intelligent process design, improved scalability across operating conditions, and enhanced robustness against experimental uncertainty. When integrated with the rapidly advancing landscape of Industry 4.0, characterized by interconnected cyber-physical systems, autonomous control architectures, and edge-cloud inference pipelines, PBDL are poised to serve as digital foundations for smart bioprocessing. In parallel, the global momentum of artificial intelligence research, including foundation models, differentiable simulation, and scientific machine learning, will continue to stimulate innovation at the intersection of chromatographic modeling and computational intelligence.

Collectively, these advancements suggest a future in which chromatographic processes operate as self-learning digital twins, capable of continuously learning from sparse measurements, predicting emergent behaviors, and autonomously optimizing separation performance in real time. As computational tools, hardware infrastructures, and scientific methodologies continue to evolve, hybrid modeling based on PBDL is expected to transition from a cutting-edge research paradigm into a practical engine of intelligent bioprocess manufacturing. Although this review focuses on chromatography, the underlying principles of PBDL are inherently generalizable. These methods hold promise for accelerating innovation across diverse bioprocess unit operations, ultimately contributing to a integrated framework for next-generation smart biomanufacturing.

6. Conclusion

This review summarizes the evolution of chromatographic modeling from fully mechanistic models to hybrid approaches based on PBDL. Three generations of PBDL methods have been identified. Surrogate solvers, as the first generation, accelerate chromatographic simulations through data-assisted physics but remain limited by dependence on pre-generated synthetic data. PINNs, as the second generation, unify physical laws and experimental data through composite loss functions, achieving improved accuracy and interpretability while facing challenges in loss balancing and numerical compatibility. DP, representing the third generation, integrates neural networks directly into numerical solvers, enabling gradient-based optimization and strong extrapolability at the cost of high implementation complexity and computational demand. Together, these methods illustrate a clear trajectory toward deeper fusion of physical knowledge and deep learning.

Looking ahead, continued advancement of PBDL is essential to reshape chromatographic science by enabling self-learning digital twins, autonomous process optimization, and intelligent bioprocess control aligned with the vision of Industry 4.0, ultimately bridging physical rigor with adaptive artificial intelligence to achieve unprecedented efficiency, accuracy, and scalability in chromatographic engineering. Although this review focuses on chromatography, the underlying principles of PBDL are broadly generalizable and hold strong potential to accelerate innovation across diverse bioprocess unit operations, contributing to an integrated framework for next-generation smart biomanufacturing.

CRediT authorship contribution statement

Yu-Cheng Chen: Writing – original draft, Visualization, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization. **Zhiyuan Chen:** Writing – original draft, Investigation. **Shi-Peng Dai:** Writing – review & editing, Investigation. **Youping Xie:** Writing – review & editing, Validation. **Shan-Jing Yao:** Writing – review & editing, Validation, Supervision, Conceptualization. **Dong-Qiang Lin:** Writing – review & editing, Validation, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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