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Integration of Parametric, Mechanistic, and AI-Based Modelling in High-Performance Liquid Chromatography: Future Prospect

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***Abstract*—Advanced liquid chromatography remains the most effective method for separating, identifying, and quantifying intricate mixtures in the fields of chemistry, engineering, and life sciences. Modifications have been implemented in chromatographic modelling and optimization to meet demands for enhanced resolution, increased speed, and improved durability. For example, transitioning from single-dimensional separations to dual-dimensional workflows. This review thoroughly examines the methodologies based on parameters and moments used to define mass transfer, dispersion, retention, and reaction kinetics in liquid chromatography systems, emphasizing their significance in method development and performance enhancement. This article explores the latest advancements in data-centric and AI-driven approaches, focusing on retention forecasting, quantitative structure–retention correlations, and automated parameter fine-tuning. The synergistic integration of mechanistic models and machine-learning techniques is explored as a feasible strategy to address challenges in complex method development, multidimensional data management, and computational costs. Some of the current issues and new trends being examined include real-time adaptive control, generative method design, and environmentally friendly chromatographic practices, but they depend on reliable online sensing, low-latency inference, and validated digital twin frameworks. This review aims to guide future progress in HPLC modelling and optimization by synthesizing theoretical, computational, and practical perspectives.**

***Keywords*—parametric analysis, reversible/irreversible, machine learning/artificial intelligence, method optimization, future perspectives**

I. INTRODUCTION

High-Performance Liquid Chromatography (HPLC) is a common method for separating complex mixtures in chemistry, pharmaceutical sciences, biotechnology, and environmental monitoring [1]. It has significant analytical power because it can separate molecules of different sizes and physicochemical properties with high resolution and reproducibility. This capability arises from its ability to operate at elevated pressures, utilize finely packed stationary phases, and accommodate versatile mobile-phase compositions [2, 3]. Recent advancements in column technology, instrumentation, and detection have significantly enhanced the utility of HPLC. Nonetheless, the increasing intricacy of analytical samples continues to pose challenges in the development of new methodologies [4].

Its robustness and user-friendliness, as well as its One-Dimensional (1D) HPLC nature, make it the preferred technique for standard analytical procedures. However, when dealing with highly complex samples that contain structurally similar or strongly retained components, the restricted peak capacity of 1D separations frequently leads to co-elution, complicating the achievement of precise quantitative outcomes [5, 6]. Comprehensive Two-Dimensional Liquid Chromatography (2D-LC), integrating two distinct separation methods into a single process, has emerged as an effective solution to these challenges by significantly enhancing resolving power and peak capacity [7, 8]. The transition from 1D to 2D separations has led chromatographic research to increasingly rely on modelling and optimization frameworks that elucidate the movement of substances, as well as retention behaviour and reaction kinetics under strongly coupled operating conditions [9, 10].

Understanding chromatographic processes and advancing method development relies heavily on mechanistic modeling [11]. Parametric analysis provides a systematic framework for quantifying the impact of operational variables, including flow rate, temperature, mobile-phase composition, column dimensions, and particle characteristics, on chromatographic performance [12, 13]. In reactive chromatographic systems, parametric models enable a thorough examination of both reversible and irreversible reaction kinetics within the column, clarifying the relationship between chemical transformation and mass transport [14]. Such analyses are crucial for contemporary systems, as elevated pressures and brief residence times enhance kinetic and dispersion effects [15].

Moment analysis has emerged as a robust framework for reduced-order modeling in chromatographic systems. This approach enables the extraction of kinetic, dispersive, and retention parameters directly from experimental data by characterizing peak evolution using statistical moments. There is no requirement to completely numerically solve the governing transport equations [16−21]. Moment-based methods offer significant advantages for parametric studies and optimization tasks, thanks to their speed and straightforward physical interpretation. The use of moment analysis in multidimensional and reactive systems has increased its importance for advanced chromatographic modelling.

Despite these advancements, the increasing intricacy of contemporary chromatographic processes, particularly in 2D-LC, poses challenges for solely mechanistic methodologies to be effective [22]. Conventional optimization methods often struggle in scenarios characterized by significant parameter interdependencies, nonlinear interactions, and expansive experimental design landscapes. In this context, the use of Artificial Intelligence

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(AI) and Machine Learning (ML) techniques has attracted significant attention as valuable tools for enhancing chromatographic modelling and method development [23, 24]. Models based on data have demonstrated significant potential in forecasting retention, identifying trends, and autonomously fine-tuning parameters [25, 26]. Integrating parametric and moment-based models within hybrid modeling strategies offers a compelling balance between physical insight and predictive performance.

Unlike previous reviews that have typically focused on either classical chromatographic theory, mechanistic model families, or recent AI-assisted method-development tools in isolation, this review provides an integrated comparative perspective across the full modelling spectrum relevant to modern HPLC. Its novelty lies in bringing together parametric analysis, moment-based reduced-order methods, mechanistic frameworks, and emerging AI/hybrid strategies within a single conceptual and practical framework. Particular emphasis is placed on how these approaches complement one another in 1D and 2D HPLC, on their differences in interpretability, computational burden, and extrapolation capability, and on how they can support current needs in multidimensional optimization, benchmarking, real-time control, and sustainable chromatographic design. In this way, the review aims not only to summarize recent developments but also to clarify the comparative roles of each modelling paradigm and to identify the most important directions for next-generation HPLC research and implementation.

II. METHODOLOGY AND SCOPE

A. Literature Search Strategy and Selection Criteria

This review is based on a survey of peer-reviewed literature published predominantly between 2006 and 2025. To improve contemporaneity and comparative rigor, particular attention was given to recent high-impact studies published in 2024–2026, especially those offering reusable datasets, explicit cross-model comparisons, cross-column generalization tests, or direct head-to-head evaluation between AI-assisted and experimentally optimized chromatographic workflows. Relevant articles were identified using Web of Science, Scopus, and Google Scholar, employing keywords such as HPLC, 2D-LC, parametric analysis, moment analysis, reactive chromatography, ML-LC, and AI-LC. Studies were selected if they satisfied at least one of the following criteria:

- Development or application of mechanistic, parametric, or moment-based models for HPLC;
- Modelling of reversible or irreversible reactions within chromatographic systems;
- Methodological advances in 1D or 2D liquid chromatography;
- Integration of data-driven or AI-based techniques for chromatographic prediction or optimization.

Further references were identified through citation tracking to ensure comprehensive coverage of essential studies and the latest developments. The focus was on efforts that deliver a quantitative understanding of parameter sensitivity, modelling assumptions, and optimization strategies, rather than solely on empirical demonstrations.

B. Parametric and Moment-Based Analysis

The primary analytical structure for this review is parametric analysis. It pertains to the systematic examination of how various operational and model parameters, such as flow velocity, temperature, mobile-phase composition, column geometry, dispersion coefficients, and reaction rate constants, influence chromatographic efficiency [27−29]. This approach enables the identification of primary transport and kinetic regimes, facilitating the logical optimization of methods across various chromatographic configurations.

The analysis of moments is explored as a supplementary tool for simplified modeling to clarify elution characteristics. Statistical moments of chromatographic peaks, including mean retention time, variance, and higher-order descriptors, offer clear insights into mass transport, dispersion, and reaction effects [30−35]. The research conducted demonstrates how moment-based methods improve the efficiency of parameter estimation, model comparison, and sensitivity analysis, particularly in complex reactive, non-isothermal, and multidimensional systems.

Although the reviewed studies collectively demonstrate the value of mechanistic, moment-based, and hybrid modelling in chromatographic optimization, direct comparison across the literature remains difficult because the published works differ substantially in separation mode, analyte system, column chemistry, operating conditions, model assumptions, and validation criteria. Consequently, this review does not treat all reported results as directly equivalent; instead, it emphasizes comparative interpretation of modelling philosophy, physical fidelity, computational burden, and practical applicability. This distinction is important because apparent performance advantages often depend on the complexity of the chromatographic system, the availability of calibration data, and the intended use context.

To avoid conceptual overlap, this review distinguishes between modelling paradigms and analytical strategies. Mechanistic, data-driven, and hybrid AI and modelling paradigms are considered the main modelling paradigms because they differ in how they represent chromatographic behaviour and generate predictions. By contrast, parametric analysis and moment analysis are treated as analytical strategies: parametric analysis examines the sensitivity of chromatographic behavior to operating and model parameters, whereas moment analysis provides reduced-order descriptors for retention, dispersion, and reaction effects and can support parameter estimation and model comparison without full numerical solution of the governing equations. This distinction helps position parametric and moment-based methods relative to mechanistic and AI-based modelling rather than presenting them as competing categories. Fig. 1 discussed in this review, organized according to their primary source of knowledge and modelling philosophy. Mechanistic models rely on governing transport and adsorption equations; parametric and moment-based approaches serve as analytical and reduced-order strategies for sensitivity analysis and parameter estimation; AI-based models learn patterns directly from data; and hybrid models combine physical structure with data-driven components, including surrogate-assisted models, physics-informed neural networks, and differentiable-physics frameworks.

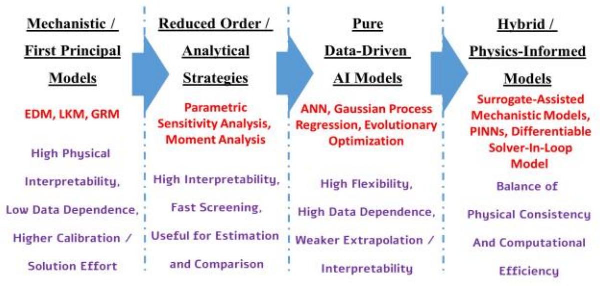

Fig. 1. Taxonomy of chromatographic modelling approaches.

Within this taxonomy, AI-based models are understood as data-driven predictors that learn input–output relationships directly from chromatographic data. In contrast, hybrid models retain an explicit physical backbone and use machine learning only to accelerate, correct, or augment parts of the mechanistic description.

C. *Mechanistic Modelling of Multidimensional*

Mechanistic models are already used to reduce costly experiments and support design decisions at production scale, while broader LC modelling and control literature frames them as tools for faster method development, improved purity/yield, and reduced solvent use [36]. Process-model literature in pharmaceutical manufacturing now explicitly discusses design, scale-up, monitoring, control, and lifecycle model maintenance as practical implementation goals [37, 38]. The review systematically compares the common mechanistic frameworks used in chromatographic analysis, including the Equilibrium-Dispersive Model (EDM), Lumped Kinetic Model (LKM), and General RATE model (GRM). Their assumptions, applicability, and limitations are analyzed in relation to parametric studies, reaction kinetics, and mass-transfer phenomena.

Table 1. Comparative summary of chromatographic modelling approaches

Model approach	**Physical interpretability**	**Computational demand**	**Data requirement**	**Extrapolation reliability**	**Suitability for 2D/complex systems**	**Real-time optimization potential**	**Main limitation**
EDM	High	Low	Low	Moderate within calibrated domain	Moderate	Moderate	Cannot represent detailed mass-transfer resistance
LKM	Moderate–High	Low–Moderate	Low	Moderate	Moderate	Moderate	Reduced physical detail due to lumped kinetics
GRM	Very High	High	Low	High when parameters are reliable	High	Limited without acceleration	Computationally expensive
Moment-based methods	High for summary descriptors	Very Low	Low	Moderate	Moderate	High for screening	Reduced detail for full profile dynamics
Pure AI / ML	Low	Low after training	High	Low outside training domain	Moderate–High	High	Weak interpretability and validation difficulty
Hybrid / PINN	High	Moderate training / low inference	Moderate	Higher than pure AI	High	High	Training complexity and loss-balancing challenges

In the realm of multidimensional chromatography, we explore the application of these models across two spatial dimensions. Our emphasis is on understanding the impacts of axial and radial dispersion, the behavior of adsorption isotherms, and the implications of boundary conditions. We examine both reversible processes, such as adsorption–desorption equilibria, and irreversible processes, including degradation or transformation reactions. Our emphasis is on the interplay between reaction kinetics and transport phenomena and their impact on separation performance [39]. Table 1 reflects how recent literature frames chromatographic model evolution: traditional mechanistic models prioritize physical detail, pure AI priorities speed and flexibility, and hybrid/PINN approaches are increasingly positioned as a compromise between fidelity and efficiency. The Supplementary Material provides comprehensive mathematical formulations, governing equations, and boundary conditions, allowing the main text to concentrate on conceptual understanding and comparisons.

From a practical perspective, the value of chromatographic modelling lies in its ability to support decisions that would otherwise require extensive experimental iteration [40, 41]. In analytical LC, mechanistic and parametric models can reduce method development time by guiding the selection of gradients, flow rates, temperatures, and column conditions before laboratory confirmation. In preparative and process chromatography, the same frameworks support scale-up, the design of pooling strategies, and the evaluation of purity–yield trade-offs under realistic operating constraints [42, 43]. Moment-based methods are especially useful for rapid screening and parameter estimation, whereas hybrid and physics-informed models are increasingly relevant for online optimization, adaptive control, and digital-twin applications in complex chromatographic workflows [44, 45]. Accordingly, the practical importance of a model should be judged not only by predictive accuracy, but also by its interpretability, computational speed, robustness, and suitability for implementation in real chromatographic systems [24].

A. *Methodologies for AI-Assisted and Hybrid Modelling*

A thorough examination of the increasing application of advanced computational techniques in separation science is provided [46−48]. We examine the application of data-driven models such as artificial neural networks, Gaussian process regression, and evolutionary algorithms for predicting retention, optimizing gradients, and classifying peaks [49, 50]. The techniques are efficient and adaptable; however, they present challenges regarding physical interpretation and extrapolation.

Hybrid models combine data-driven, descriptive models with process knowledge captured in mechanistic models [51]. They provide better process understanding and allow extrapolation, with lower demands for data quality and quantity than purely data-driven models [52]. Hybrid models also allow the use of mechanistic knowledge when the prerequisites for purely mechanistic models are not met, i.e., when mechanisms are insufficiently established in equations [53]. Hybrid models described in the literature are predominantly used for upstream production [54−56], with only a few examples of hybrid modeling in digital-signal-processing [57, 58]: Namely, Narayanan et al. learned the chromatographic unit behavior by a combination of neural network and mechanistic model while fitting suitable experimental breakthrough curves, Joshi et al. used a mechanistic model to simulate the analytical separation for the design-of-experiment and build with the results an empirical model [59], and Creasy *et al.* [60] learned the adsorption isotherm model from batch isotherm data by using interpolation techniques.

The present review focuses specifically on Physics-Informed Neural Networks (PINNs). Beyond computational efficiency, physics-informed hybrid models may also help address regulatory concerns associated with purely black-box AI. Because PINNs embed governing equations, conservation relationships, and boundary conditions into the training process, their outputs are more likely to remain physically plausible and scientifically traceable [61]. It is important in regulated analytical settings, where model acceptance depends not only on predictive accuracy but also on credibility, robustness, transparency, and validation for a clearly defined context of use. Therefore, PINNs do not eliminate regulatory requirements, but they provide a more defensible framework for model development, extrapolation within a physically meaningful operating region, and lifecycle validation than unconstrained data-driven models [62]. These networks can directly embed mass-balance and transport equations into their learning architectures, making it easier to solve forward and inverse chromatographic problems. The studies examined show that hybrid methods can significantly reduce computational costs while maintaining physical consistency. It supports real-time optimization and adaptive control [23, 25, 63].

A more critical comparison of existing modelling strategies is necessary, as each framework balances physical fidelity, computational cost, data requirements, and practical usability differently [24, 64]. Mechanistic models such as EDM and LKM are attractive for rapid parametric screening, but they rely on simplifying assumptions that can limit fidelity under strong mass-transfer or non-ideal conditions [65]. In contrast, GRM offers higher physical realism and stronger scale-up relevance, but at substantially greater computational expense [24]. More detailed mechanistic models are useful, but they must address parameter identifiability and uncertainty propagation before they can be extrapolated reliably. Purely data-driven AI models are fast and flexible once trained, yet their interpretability and extrapolation remain limited. Hybrid and physics-informed approaches, including PINNs, attempt to bridge this gap by preserving mechanistic consistency while reducing simulation time and improving adaptability for optimization and control [66]. For example, recent PINN-based chromatographic studies have reported substantial reductions in computation time while preserving predictive fidelity; one GRM-PINN study reduced offline fitting time from 2608.6 s to 110.7 s and completed online simulations in 12–14 s, illustrating the practical value of hybrid acceleration for real-time optimization [67].

Recent literature shows that the field is moving from proof-of-concept AI applications toward more rigorous comparative evaluation. In addition to broad reviews of AI-assisted LC method development and physics-based deep learning, several recent studies provide benchmark-style evidence by comparing multiple algorithms on shared datasets, testing transferability across stationary and mobile phases, or directly contrasting AI-generated conditions with experimentally refined workflows. These studies indicate that machine-learning models can substantially accelerate retention prediction and method screening, but they also show that practical performance still depends on dataset diversity, validation design, uncertainty awareness, and experimental confirmation. Accordingly, the most informative recent contributions are those that combine methodological novelty with transparent comparative evaluation.

III. PROBLEMS AND LIMITATIONS

Comprehensive 2D-HPLC provides significant improvements in resolving power; however, various challenges still hinder its regular application and the predictive accuracy of related modeling frameworks [68]. A major problem is that developing methods is hard. Unlike 1D separations, 2D HPLC requires simultaneous optimization of two separation dimensions. These dimensions include column chemistries, mobile-phase compositions, gradients, flow rates, and modulation parameters. The strong connection between these variables makes systematic optimization more difficult and often requires extensive trial-and-error, especially for very complex samples [69]. In addition, following the best practices for review articles in separation science, we have intentionally limited the use of mathematical derivations and detailed equations to the Supplementary Material.

An ongoing challenge remains the effective transfer of analytes across different dimensions. When modulation times, transfer volumes, or sampling frequencies are not optimized, the analyte may experience dilution, under sampling, or breakthrough, leading to challenges in achieving accurate and precise results. The impact is more pronounced for trace-level components and in rapid ultra-HPLC conditions, where the narrow peak widths hinder effective modulation. Sample preparation and matrix effects present significant challenges for practical application. Intricate matrices lead to overlapping interferences, column contamination, and diminished signal strength, requiring carefully refined pretreatment methods. While these steps are essential, they introduce additional time, costs, and variability to the analysis, often complicating the overall workflow in biological and environmental applications [70].

Another factor contributing to the limited use is the high cost of the equipment and the need for specialized expertise. Advanced 2D-HPLC systems require sophisticated hardware, software, and data-processing expertise, making them more challenging for typical analytical laboratories to implement. Existing obstacles complicate the generation of extensive, varied datasets, which are essential for robust model validation and the advancement of artificial intelligence [24]. From a modeling perspective, mechanistic approaches such as equilibrium-dispersive, lumped kinetic, and general rate models rely on simplifying assumptions, including ideal packing, linear adsorption, and isothermal operation [71]. In real-world applications, variations arising from column inconsistencies, nonlinear adsorption behaviour, and temperature variations can reduce the reliability of predictions, particularly when models are applied outside their calibrated parameter ranges or during extrapolation or scaling [72].

Machine-learning methods add new problems that need to be solved. Even though data-driven models can accurately capture nonlinear trends, their performance depends heavily on the quality and representativeness of the training data. Extrapolation beyond the training domain remains unreliable, and mechanisms are hard to validate and obtain regulatory approval for many models because they are hard to understand. The lack of standardized, publicly available benchmarking datasets further impedes objective comparison and reproducibility in AI-based chromatographic studies [73, 74]. Although data-driven models can capture nonlinear trends effectively, extrapolation beyond the training domain remains uncertain, and limited interpretability can complicate mechanistic validation and regulatory acceptance; however, hybrid physics-informed approaches such as PINNs may partially mitigate these concerns by constraining predictions with governing physical laws and thereby improving model credibility and validation readiness [61, 75]. It is safer to say that PINNs help address or partially mitigate regulatory hurdles, rather than claim they fully overcome them. Current FDA guidance frames AI review around a risk-based credibility assessment for a defined context of use; the EMA emphasizes sufficient technical detail, data integrity, and generalizability; and ICH Q14 supports science- and risk-based lifecycle management for analytical procedures, including multivariate ones [76]. Although recent studies increasingly report cross-model comparisons and reusable datasets, objective benchmarking in chromatography remains less mature than in many other modelling fields, making reproducibility, transferability, and fair comparison continuing methodological priorities.

Concerns about sustainability are becoming increasingly important. Chromatographic workflows have a significant environmental impact because they use large volumes of solvents, rely on hazardous organic eluents, and generate substantial waste. Researchers are currently exploring greener stationary phases, alternative solvents, and ways to reduce waste. However, it is still hard to use these for high-performance, multidimensional separations without losing strength and resolution. These limitations collectively underscore the necessity of integrated strategies that combine mechanistic understanding, data-driven modelling, and sustainable design principles, thereby motivating the future directions elaborated upon in the subsequent section.

Several recent studies illustrate these limitations quantitatively. For instance, in a 2025 comparison between an AI-predicted and an experimentally optimized HPLC method, the AI-generated workflow required human refinement. It produced markedly longer retention times for the target analytes (7.12, 3.98, and 12.12 min) than the optimized in-lab method (0.95, 1.36, and 2.82 min), while also consuming more solvent and showing poorer greenness metrics [77]. Likewise, although recent retention-prediction studies have improved cross-column generalization, available benchmark datasets remain relatively limited; one recent RP-HPLC study reported a database of 51 compounds and 1,790 retention-time values across 20 stationary phases, which is valuable but still modest relative to the diversity needed for broad chromatographic generalization [78]. Even in hybrid and physics-informed modelling, computational advantages do not eliminate all limitations: a recent PINN-based chromatographic control study reduced offline simulation time from 2608.6 s to 110.7 s and completed online simulations in 12–14 s, yet such models still require stable training, appropriate physics constraints, and careful validation before reliable deployment [66]. These examples show that current limitations are not only theoretical concerns but also directly affect runtime, transferability, solvent use, and real-world applicability.

IV. FUTURE DIRECTIONS

Future progress in HPLC modelling depends less on simply combining more tools and more on resolving several persistent methodological bottlenecks. The most critical among these are the limited transferability of model parameters across systems, uncertainty in extrapolation beyond calibrated operating spaces, insufficient treatment of parameter identifiability, and the absence of standardized benchmarking datasets for fair model comparison. Accordingly, future research should prioritize models that are not only accurate but also interpretable, robust, computationally efficient, and suitable for deployment in real analytical workflows.

Improvements in the modelling of modulation and transfer processes will become increasingly important for advancing multidimensional chromatography. To optimize modulation time, sampling frequency, and interface design, it will be important to incorporate peak sampling theory, dilution effects, and transfer efficiency directly into mechanistic and hybrid models. These developments are particularly important for swift ultra-HPLC and trace-level analyses, where peak widths approach the limits of practical modulation. Enhancing traditional frameworks such as EDM, LKM, and GRM models to better represent real chromatographic systems poses a notable modelling challenge. Future models should increasingly integrate nonlinear adsorption, column variability, non-isothermal processes, and interconnected reaction–transport dynamics. At the same time, ensuring parameter identifiability and quantifying uncertainty requires a more structured methodology to support reliable extrapolation and scaling.

The integration of AI is expected to become more prominent, particularly when paired with mechanistic models. Combining hybrid approaches with physics-informed techniques offers an efficient and precise means to forecast retention, dispersion, and reaction kinetics. Future research should focus on improving training stability, ensuring generalization across various column chemistries, and enhancing the interpretability of AI models. Additionally, there is a need to develop standardized, publicly available benchmarking datasets for chromatographic applications. A crucial domain of investigation involves automation and real-time adaptive control. Integrating online sensors with predictive models and AI algorithms could enable closed-loop adjustments to gradients, flow rates, and modulation parameters, dynamically responding to variations in sample composition or system performance.

The features under discussion closely resemble advances in digital twins for chromatographic systems, potentially enhancing the productivity and reliability of both analytical and preparative tasks.

Ultimately, the emphasis on sustainability will increasingly shape the evolution of chromatography. Utilizing parametric modelling can enhance sustainability by enabling the selection of optimal solvents, reducing solvent use, prolonging column lifespan, and balancing performance and environmental considerations. To optimize HPLC in light of emerging environmental and regulatory demands, it is essential to develop sustainable stationary phases and implement low-waste workflows, complemented by predictive modeling. Therefore, the main challenge is not merely to develop more sophisticated models, but to establish modelling frameworks that remain physically credible, computationally practical, quantitatively comparable, and experimentally transferable across realistic chromatographic conditions.

A key requirement for future chromatographic modelling research is stronger translation from algorithmic development to deployable workflows. In practice, this means models should be evaluated based on whether they can shorten development timelines, reduce solvent and sample consumption, support analytical quality-by-design strategies, enable Process Analytical Technology (PAT), and support real-time or near-real-time operational decisions. For preparative and bioprocess chromatography in particular, the most useful models are likely to be those that can support control of pooling windows, detect process drift, and remain maintainable over the product lifecycle.

V. CONCLUSION

The evolution of HPLC is evident as it transitions from a primarily 1D analytical approach to a multidimensional, model-driven, and increasingly data-assisted separation platform. It highlights that parametric analysis and moment-based methodologies provide robust, physically interpretable frameworks for clarifying transport, dispersion, and reaction effects in both 1D and 2D systems, thereby aiding the development and optimization of logical methods. The implementation of 2D HPLC significantly enhances the resolution of complex samples; however, it requires sophisticated modelling, effective data management, and meticulous consideration of system behaviour under non-ideal conditions to achieve optimal performance. The growing application of AI, particularly in hybrid and physics-informed approaches, presents innovative opportunities to enhance retention prediction, optimize operating conditions, and manage complex multidimensional datasets. To ensure ongoing advancement, it is essential to integrate mechanistic understanding, data-centric methodologies, and principles of sustainable design more effectively. It will ensure that future chromatographic systems are not only more powerful but also more reliable, efficient, and accessible. Utilizing parametric and moment-based analysis, combined with mechanistic modelling and AI, establishes a cohesive approach to understanding, advancing, and safeguarding the future of HPLC as it transitions towards multidimensional, data-centric, and sustainable separation systems. Ultimately, the practical success of chromatographic modelling will depend on how effectively it improves real method development, process robustness, scale-up, control, and sustainability, rather than on theoretical sophistication alone.

CONFLICT OF INTEREST

The author declares no conflict of interest

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