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Practical Teaching of Modeling Tools for Ion-Exchange Chromatography: A Case Study

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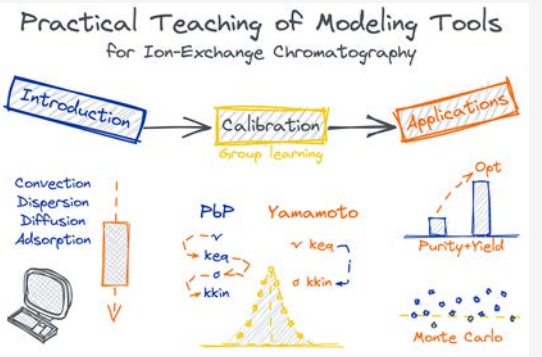
ABSTRACT: The utilization of modeling tools has gained significant attention recently. These models typically involve a series of partial differential equations, which can be challenging for novice modelers. This paper presented an approach in practical teaching of modeling tools for ion-exchange chromatography with three parts: model introduction, model calibration through group learning using different calibration strategies, and model applications. This approach was integrated into the traditional bioseparation engineering curriculum as an activity, using the separation of monomer−dimer mixtures of monoclonal antibodies as an example. Results of competitive group learning and the Wilcoxon test revealed that the parameter-by-parameter method was more user-friendly than the Yamamoto method for novice modelers to obtain reasonable model parameters quickly. Then, students used the well-fitted model for process optimization and explored the effects of process parameters and material input variation on the chromatography process, which helped students appreciate the critical role of time and material savings achieved through modeling tools. Finally, the student questionnaire results revealed that over two-thirds of the students gave positive feedback on the activity. Through this practical teaching, students became familiar with chromatography modeling tools, moving away from the tedious formulaic descriptions found in traditional modeling courses. This well-designed activity can be expanded from academia to industry, transforming the novice modelers into experienced modelers who can meet the high demands of the modern biopharmaceutical industry.



KEYWORDS: *Upper-Division Undergraduate, Graduate Education/Research, Analytical Chemistry, Computer-Based Learning, Biotechnology, Chromatography, Drugs/Pharmaceuticals, Proteins/Peptides*

As our understanding of bioprocess separation deepens, the tools used for process development, optimization, and characterization are shifting from traditional experimental methods to mechanistic modeling approaches.[1] However, teaching these models, which often involve complex partial differential equations, can be challenging for engineering students and industry employees with limited experience in mathematics and physics. Therefore, it is crucial to design an attractive practical teaching approach to make the dull equations alive. By extensively exploring and leveraging available model tools, we have designed an approach for the practical teaching of ion-exchange chromatography modeling tools. This teaching aims to transform the novice modelers into experienced modelers capable of meeting the high demands of the biopharmaceutical industry, while complementing their understanding of fundamental theoretical knowledge.

Some popular ion-exchange chromatography modeling tools include CADET,[2] GoSilico,[3] ChromaTech,[4] and Orbit.[5] These user-friendly tools offer instructional materials, including model introduction and software exercises, model calibration, and model applications. Although these tools have simplified the requirements for novice modelers in terms of mathematics and physics knowledge, mastering their usage remains challenging, particularly in achieving accurate and reliable model calibration. When confronted with numerous options for calibration methods, they often lack prior knowledge to determine which method is preferable. Some examples of model calibration methods include CADET-Match in CADET,[6] a systematic reduction of undetermined model parameters in GoSilico,[7] searching for reasonable initial guesses of the inverse method in ChromaTech,[8] and an automatically calibrated system in Orbit.[9] These calibration strategies can be classified into two main categories: fully inverse method (CADET) and inverse method combined with the Yamamoto method,[10] i.e., the combined Yamamoto method (GoSilico, ChromaTech, and Orbit).[11] Nevertheless, both approaches have limitations, encountering ill-posed problems and limited applicability under diluted conditions.

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To address these issues, we have recently developed a novel parameter-by-parameter (PbP) method for steric mass action (SMA) model calibration.[12,13] The PbP method features a one-by-one calibration strategy that yields physically meaningful parameters. Furthermore, it can be easily implemented using Microsoft Excel spreadsheets, known for their pedagogical potential in chromatography.[14−16] Therefore, in this activity, we would employ spreadsheets to implement the PbP method and utilize group learning to compare different calibration methods, assisting novice modelers in selecting the most suitable approach.

Once calibrated, the models can be applied to various scenarios, unlocking their full potential. One of the most intuitive applications is process optimization, where key performance criteria like purity, yield, and productivity serve as indicators of efficiency and quality in chromatographic separations and are optimized based on design, operating, and model parameters. This helps novice modelers grasp the time and cost benefits in contrast to traditional experimental methods. A classic optimization scenario for ion-exchange chromatography is finding the optimal salt gradient elution conditions.

Another important application of modeling tools is process characterization, allowing novice modelers understand the impact of process parameters and material input variations on the processes from a modeling perspective. For instance, in ion-exchange chromatography, modeling tools can provide insights into the impact of loading concentration on the chromatographic process and resulting product quality.

■ ACTIVITY DESCRIPTION

This paper introduces an approach for the practical teaching of modeling tools for ion-exchange chromatography. This approach is designed for novice modelers who have a foundational understanding of chromatography's basic principles. The main goals of this teaching method are to familiarize novice modelers with advanced modeling concepts and to develop their skills in model calibration and applications. To achieve these goals, the approach consists of three key components: model introduction, model calibration through group learning using different calibration strategies, and model applications including process optimization and characterization. On average, the entire process took approximately 4 h to complete, including 1 h for model introduction, 1.5 h for model calibration, and 1.5 h for model applications.

For this teaching, we utilized a well-designed Excel spreadsheet and the freely accessible GoSilico Student Edition software, which features a friendly graphical user interface. Students were required to complete specific model tasks using this software and record their results in a provided template (see the Supporting Information). Then, the completed template was submitted through the online learning platform. The collected data included results of model calibration (e.g., calibrated parameters and corresponding elution curves) and results of model applications (e.g., optimal conditions and corresponding elution curves).

To assess significant differences in group learning between the two groups, the Wilcoxon test was conducted at a significance level of 5%, which is suitable for non-normally distributed data.

This approach was integrated into the bioseparation engineering curriculum offered at the College of Chemical and Biological Engineering, Zhejiang University, as an activity. It was conducted twice: once in the summer of 2022 for 24 upper-level undergraduate students and again in the spring of 2023 for 25 master's and 14 Ph.D. students, totaling 63 participants. To account for variations in educational backgrounds among the students, we would differentiate their academic levels when presenting certain results.

■ METHODS

Model Introduction

The activity began by introducing ion-exchange chromatography models. Ion-exchange chromatography is an important bioseparation technology for purifying chargeable molecules such as proteins.[17] Figure 1 illustrates the retention of components with stronger binding to the solid phase in the liquid phase, resulting in separation. During the process, the phases undergo different mass transfer (e.g., convection, dispersion, diffusion, and adsorption). Assuming an instantaneous equilibrium between the phases, the interparticular concentration is equal to the average intraparticular concentration. Thus, the driving force for diffusion is neglected, and all effects caused by the axial dispersion and other diffusion effects are lumped into an apparent axial dispersion coefficient to describe peak broadening.[18] This assumption yields the equilibrium dispersive model, which would be used in this work. Additionally, the adsorption equilibrium was described by the SMA model, with four parameters (characteristic charge ν, equilibrium coefficient k_{eq}, shielding factor σ, and kinetic coefficient k_{kin}). This model is suitable for modeling of protein purification by ion-exchange chromatography because it accounts for the salt dependence of protein adsorption and the steric shielding of binding sites caused by their ternary structure under nonlinear conditions.[19]

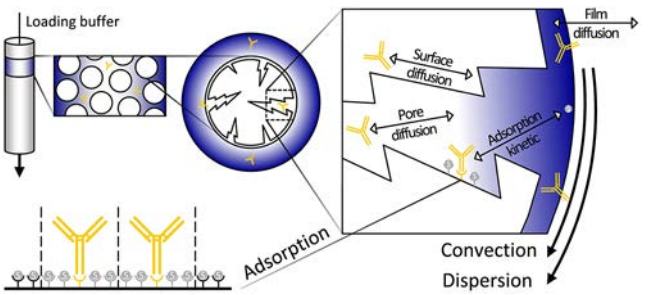

Figure 1. Protein adsorption on ion-exchange resin with steric mass action. Colored areas: solid (white) and liquid (purple). Gray circles: sodium ions. Y-type yellow structures: proteins. Colored binding sites: available (black), shielded by steric mass action (gray), and bound by proteins (yellow).

Model Calibration

The combination of equilibrium dispersive and SMA models yielded three classifications of model parameters: system parameters, column-specific parameters, and SMA parameters. In this course, only the SMA parameters were estimated. The remaining parameters were provided directly. All students were randomly assigned to employ either PbP or combined Yamamoto methods to calibrate the SMA model.

The PbP method involves the calculation of retention times and features a one-by-one calibration strategy: (1) first linear regression (LR1) for ν, (2) second linear regression (LR2) for k_{eq}, (3) linear approximation (LA) for σ, and (4) inverse method for k_{kin}.

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The combined Yamamoto methods is valid only under diluted conditions and yields initial guesses for high loadings: (1) Yamamoto correlation for determined values of ν and initial guesses of k_{eq} and (2) inverse method for σ and k_{kin}.

Model Applications

Three model applications were explored after model calibration. First, students determined the optimal operating parameters (salt gradient) to maximize both purity and yield. Second, they examined the effects of design parameter (column length), operating parameter (residence time during elution phase), and model parameter (dispersive coefficient) using the one-factor-at-a-time method. Third, they investigated the impact of material input variation (loading concentration) through Monte Carlo simulation.

Modeling Tools and Software

The GoSilico Student Edition software was provided kindly by Cytiva, which has various out-of-the-box modeling tools of chromatographic processes, including the well-established model combinations (equilibrium dispersive and SMA models), the combined Yamamoto method, the heuristic and deterministic algorithm, the one-factor-at-a-time method, and Monte Carlo simulation (Latin hypercube sampling). Additionally, students were provided with a well-designed Excel spreadsheet (see the Supporting Information) to use the PbP method. Figure 2 shows a step-by-step instruction of modeling tools for model calibration and model applications.

Experimental Data

Seven elution curves were obtained from the literature[20,21] (see the Supporting Information), involving the separation experiments of monomer−dimer mixtures of monoclonal antibodies. The sample contained 72% mAb (M_r = 150 kDa) and 28% dimer (M_r = 300 kDa). The ion-exchange separation experiments were performed in a column with a diameter of 0.5 cm and a length of 5.0 cm, with a total porosity of 0.858 and an ion-exchange capacity of 200 mM. A linear gradient from 20 to 320 mM Na^+ was applied at a flow rate of 0.5 mL/min. The apparent dispersive coefficient was 0.79 mm/s^2. Table 1 presents the loading conditions and gradient lengths for the seven experiments.

HAZARDS

There are no hazards associated with this computer-based course.

RESULTS

Model Introduction and Software Exercises

This section introduced the basic principles of chromatographic models, including how to derive them, the meaning of various parameters, and their effects on the chromatographic process. It also provided an overview of each subpage and common operations in GoSilico. Note that students were assumed to be familiar with manipulating experimental data using Microsoft Excel spreadsheets.

Model Calibration

The students were divided into two groups for model calibration: one group used the PbP method, and the other group used the combined Yamamoto methods, as illustrated in Figure 2. The resulting calibration data was organized into boxplots and is visualized in Figure 3.

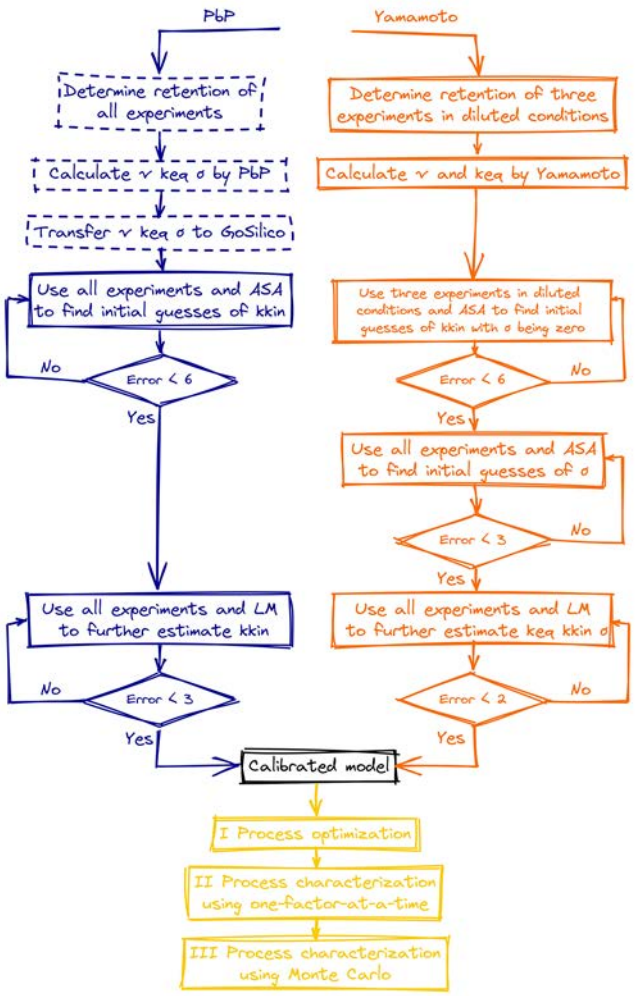

Figure 2. Step-by-step instruction of modeling tools for model calibration using parameter-by-parameter (blue) and Yamamoto (orange) methods and model applications (yellow). ASA: a heuristic algorithm named adaptive simulated annealing. LM: a deterministic algorithm named Levenberg−Marquardt. Implementation: Microsoft Excel spreadsheets (dashed boxes) and GoSilico (solid boxes).

Table 1. Bind-and-Elute Experiments about the Separation of Monomer−Dimer Mixtures of Monoclonal Antibodies for Model Calibration

No.	Loading Amount (g/L column)	Loading Volume (mL)	Gradient Length (CV)	Ref
1	2	0.1	15	20
2	2	0.1	25	20
3	2	0.1	40	20
4	4	0.97	25	21
5	10	2.4	25	21
6	20	4.9	25	21
7	40	9.7	25	21

Figures 3a and 3b show ν averages that are in close proximity to the reported values of 10.2 and 14.8,[20] respectively, for monomers and dimers. Figures 3c and 3d illustrate that k_{eq} averages of the Yamamoto group are generally higher than those of the PbP group because k_{eq} was further determined by the inverse method in the Yamamoto group. Figures 3e and 3f demonstrate that there was no significant difference in monomers' σ between the two student groups, but the PbP

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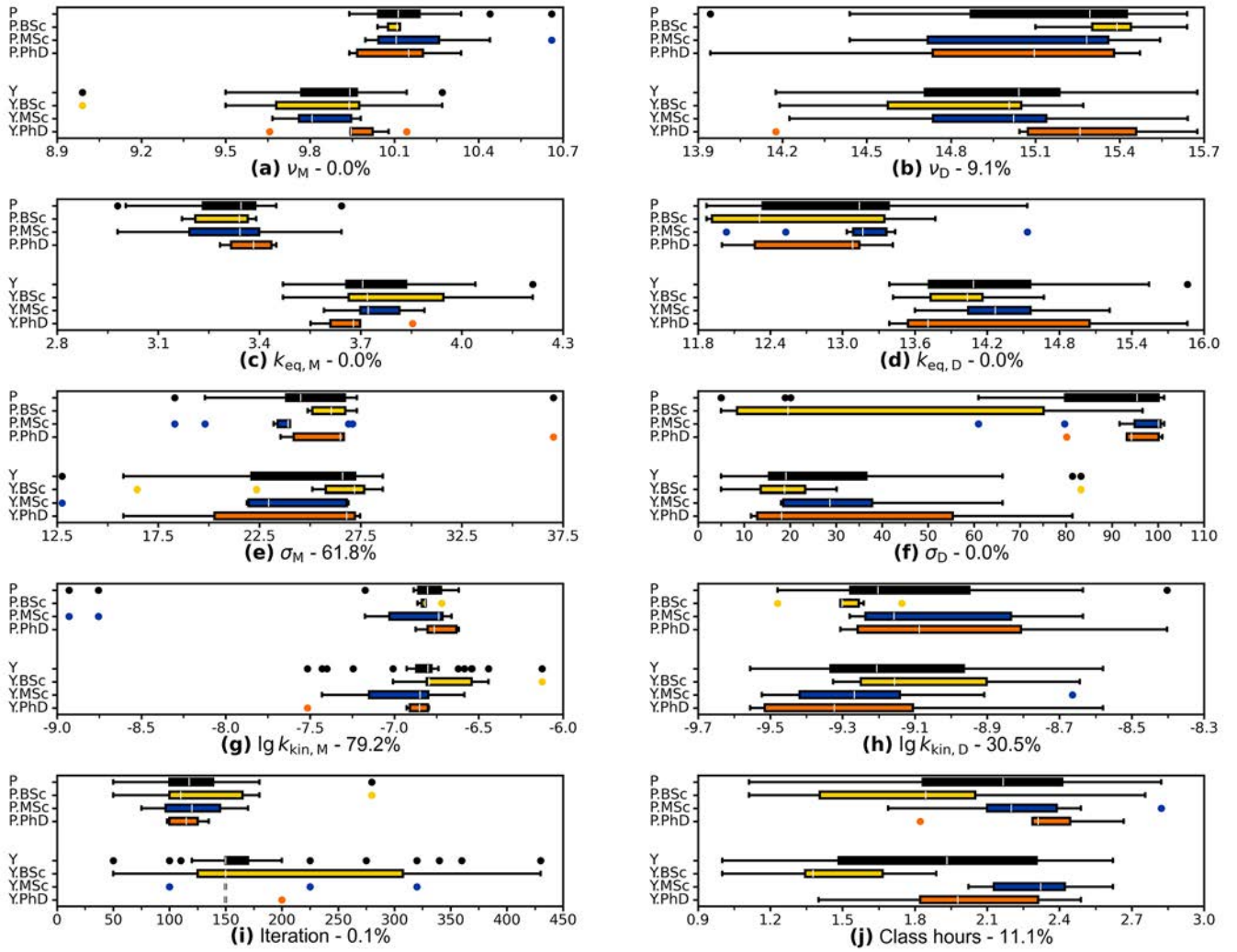

Figure 3. Model calibration results of parameter-by-parameter and Yamamoto groups. Colored bars: all (black), bachelor's (B.Sc., yellow), master's (M.Sc., blue), and Ph.D. (orange) students. Each subplot's bottom shows the corresponding subtitle with a p-value description: model parameters (a–h), number of iterations (i), and class hours for model calibration (j).

(LA) group exhibited an average σ of 79.2 for dimers, which is twice that of monomers (29.1). Figures 3g and 3h represent that there was no significant difference in k_{kin} between the two student groups. Since the dimension of this constant is logarithmic, it was compared after taking the logarithm.

Figure 3i presents that the PbP method requires significantly fewer iterations with an average of 124 compared to 181 for the Yamamoto group. Figure 3j illustrates that the students in the PbP group require more class hours to calibrate the models compared to the other group, although there are no significant differences between the two groups. Figure 4 presents the elution curves generated by the average SMA parameters (Figure 3a–h). The calibration errors of PbP and Yamamoto groups are similar.

Model Application I: Process Optimization

All students applied the calibrated model to determine the optimal salt gradient for maximizing both purity and yield in experiment No. 6 (a benchmark experiment for all model applications) using GoSilico. The optimization results were presented in groups to highlight the significance of the calibration approaches.

Figures 5a and 5b show the optimal high-salt buffer ratios at the gradient start and end, respectively. Most optimal ratios are at a moderate level between 20% and 60% high-salt buffer, indicating that the salt concentration used for process optimization is appropriate. Figure 5c shows the optimal ratio change in high-salt buffer, with mean values 18.6% and 23.8% for the two groups of students, respectively. Figure 5d illustrates that the optimal objective function values (sums of yield and purity) are almost 100% for both groups.

Model Application II: Process Characterization Using the One-Factor-at-a-Time Method

This part allowed students to employ the one-factor-at-a-time method in GoSilico to explore the effects of column lengths, residence times during the elution phase, and dispersive coefficients on chromatographic processes using their established model. Benchmark experiments were considered as reference to present typical results.

Figure 6a illustrates the effect of column lengths, revealing that longer columns lead to higher resolution and more apparent axial dispersion phenomena because the effect of column length on dispersive coefficients was considered. Figure 6b demonstrates the effect of residence times, indicating that larger

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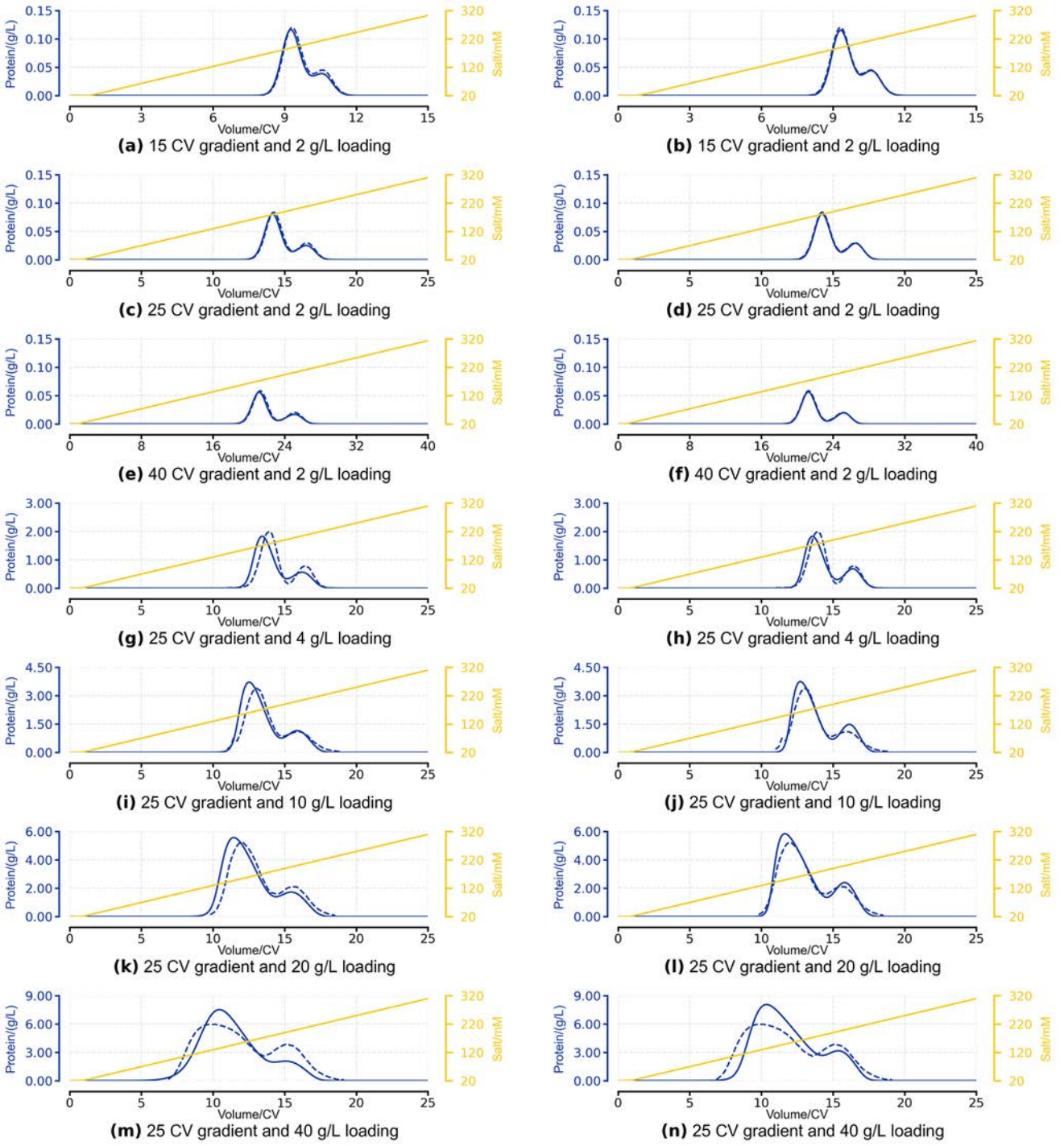

Figure 4. Elution curves of calibration experiments (blue dashed lines) and simulations of average model parameters (blue solid lines) for students in parameter-by-parameter (left) and Yamamoto (right) groups. Each subplot's bottom shows gradient and loading conditions. Yellow lines: salt gradient at column outlet. All curves were simulated by GoSilico and replotted by Matplotlib.

residence times resulted in higher resolution with taller peaks. Figure 6c represents the effect of dispersive coefficients demonstrating that larger coefficients led to more apparent axial dispersion phenomena and broader peaks.

Model Application III: Process Characterization Using Monte Carlo Simulation

In the previous section about process optimization, a question was left unanswered: how sensitive and robust are the optimal operating conditions found by the model? To address this question, the students tried to use Monte Carlo simulation in GoSilico.

Figure 7a depicts a criticality assessment of dimer loading concentration. As the dimer loading concentration increased from 1 to 2 times the benchmark experiment, the monomer purity decreased. If the monomer purity specification is 90%, the product quality would be unsatisfactory when the dimer concentration varied by 1.8 times the benchmark. Figure 7b illustrates results of 100 Monte Carlo simulations using

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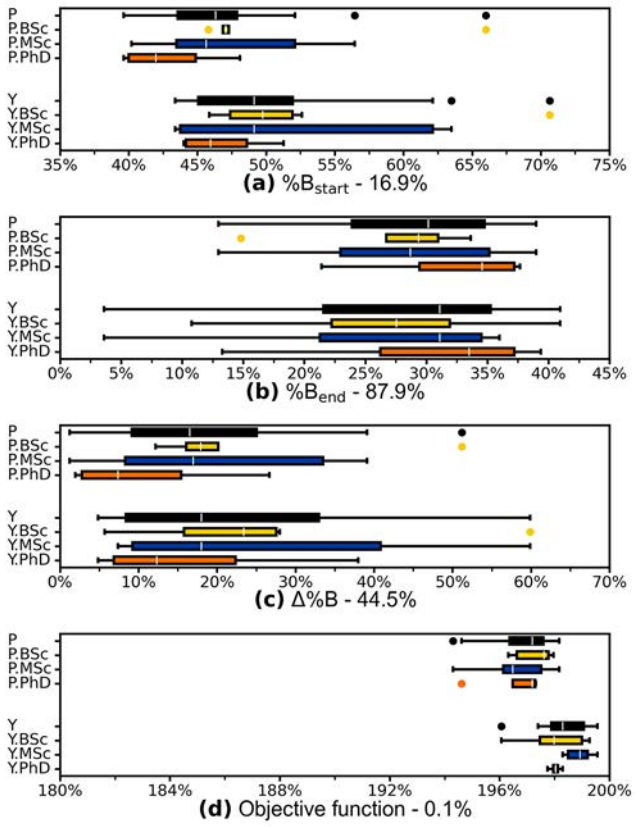

Figure 5. First application results of process optimization for parameter-by-parameter and Yamamoto groups. Colored bars: all (black), bachelor's (B.Sc., yellow), master's (M.Sc., blue) and Ph.D. (orange) students. Each subplot's bottom shows the corresponding subtitle with a p-value description: high-salt buffer ratios at gradient start (a) and end (b), ratio change (c), and objective function (d).

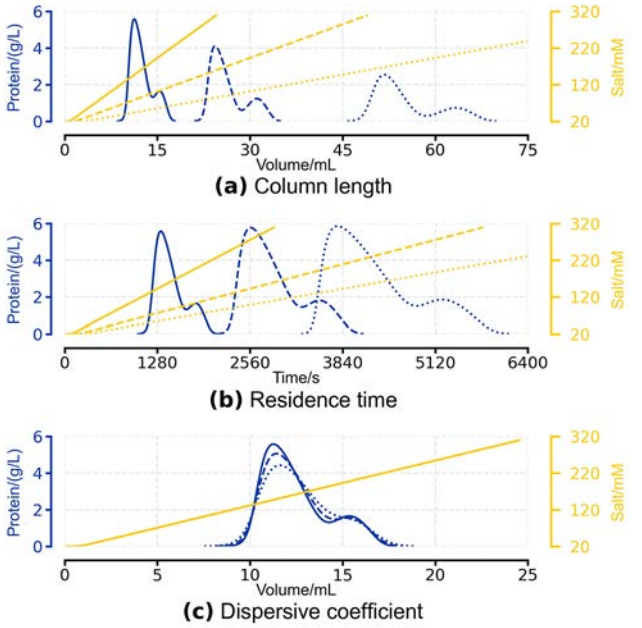

Figure 6. Second application results of process characterization of column lengths (a), residence times during the elution phase (b), and dispersive coefficients (c) using the one-factor-at-a-time method. Solid lines: 1× benchmark experiments. Dashed lines: 2× benchmark experiments. Dotted lines: 4× benchmark experiments. Blue lines: elution curves. Yellow lines: salt gradient at the column outlet. All curves were simulated by GoSilico and replotted by Matplotlib.

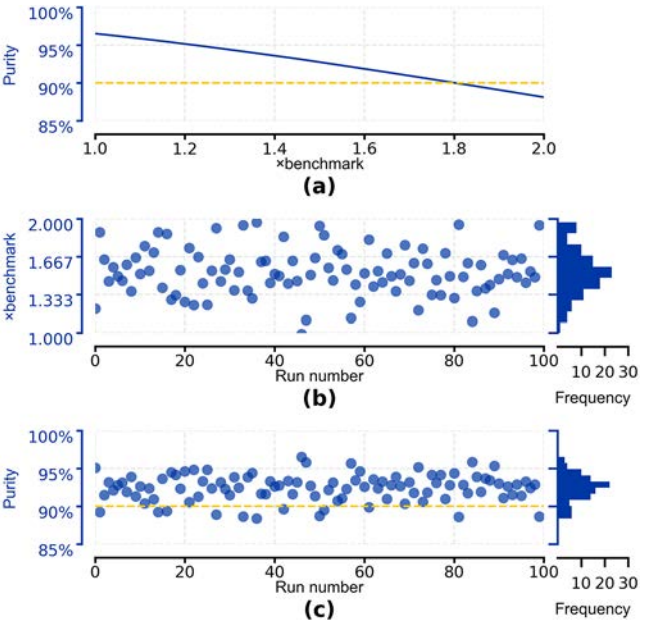

Figure 7. Third application results of process characterization: (a) criticality assessment of dimer loading concentration, (b) simulated variations of dimer loading concentration, and (c) simulated variations of product purity. Yellow lines: product purity specification. All data were obtained by GoSilico and replotted by Matplotlib.

GoSilico, which modeled variations of dimer loading concentration during ion-exchange separation in real production processes. Figure 7c shows that the product purity varied between 88.4% and 96.5% in the 100 production processes. According to the frequency distribution chart, the product did not meet the purity specification in approximately 12 out of 100 simulations.

EVALUATION OF PRACTICAL TEACHING AND STUDENTS' PERFORMANCE

According to our survey, out of 63 students, 59 had never been exposed to any form of chromatographic modeling tools. Through our meticulous guidance and the students' high effort and commitment, over 95% of the students (60 students) were able to promptly complete the assigned modeling tasks in class.

We evaluated the students' performance about completing the modeling tasks from multiple perspectives. For model introduction, we engaged the students in classroom discussions to help them identify the influence of model parameters on the chromatographic process and derive the chromatographic model equations together. For model calibration, we primarily analyzed the reasonableness of the parameters calibrated by the students, considering whether the errors were within an acceptable range. For model applications, we assessed the reasonableness of the optimal operating conditions identified by the students, as well as the improvement in yield and purity after optimization. Additionally, we encouraged the students to utilize the modeling tools to explore the impact of model parameters on the chromatographic process.

Model Calibration

Most students have learned how to calibrate chromatographic models using modeling tools and obtained well-fitted models.

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However, approximately 14% of the students still obtained unsatisfactory calibration results. Among them, four students did not strictly follow the modeling process and thereby obtained significantly large calibration errors.

For group learning, the equations of PbP (LR1) and combined Yamamoto methods were found to be completely identical for estimating ν. Therefore, there should not have been any significant differences in results between both groups. However, surprisingly, the p-value of Figure 3a indicates significant differences between the methods. This difference might be due to the disparities in retention time determination between the two software programs rather than differences in the methods themselves. Regarding the estimation of σ, the PbP group provided results that were more physically meaningful, reproducing the parameter's twofold relationship (see Figure 3f) between monomers (150 kDa) and dimers (300 kDa), in line with the fact that dimers exhibit stronger steric shielding. This aspect aided students in developing an understanding of the physical significance of model parameters, which is one of the primary objectives of our practical teaching.

Additionally, we observed varying levels of interest in modeling tools among students with different academic backgrounds. For instance, when we suggested that students attempted to calibrate the model with fewer iterations, undergraduate students were more willing to try, while graduate students tended to follow the standard iteration number of 150, as shown in Figure 3i. Furthermore, Figure 3j illustrates that undergraduate students achieved the fastest completion time for model calibration compared to other students. This discrepancy may be attributed to their major in the field of biotechnology, which granted them a deeper understanding of chromatography concepts.

Moreover, an analysis of students' software operation logs revealed that the Yamamoto group spent a significant amount of time determining initial guesses for the inverse method. This implied that employing the PbP method would be more user-friendly in teaching novice modelers to obtain reasonable model parameters quickly.

Model Applications

In this section, students conducted three model applications. For process optimization, all students were taught to find the optimal salt gradient. Based on our experience, we analyzed the rationale behind their identified optimal conditions. We discovered that despite dividing the students into two groups and using different calibration methods for the models, they generally obtained similar optimal conditions. This not only confirmed the students' proficiency in process optimization but also suggested that the system already had a high-resolution separation prior to optimization, limiting the potential for significant improvements through the optimization. Nonetheless, the students still appreciated the critical role of time and material savings achieved through the use of modeling tools compared to traditional experimental methods for enhancing process performance.

For process characterization using the one-factor-at-a-time method, the students gained an understanding of how process parameters impact the chromatography process from a modeling perspective. This served as a complementary approach to the theoretical learning in the first part. Inspired by Marson and Torres,[22] we included several multiple-choice questions in the final exam of the bioseparation engineering course, asking students, "which chromatogram can be expected if the convection/dispersion/diffusion/adsorption term in the equation is altered?" Results demonstrated that 100% of the students were able to select the correct answer, indicating that the use of modeling tools contributed to enhancing students' understanding of the chromatographic process.

For process characterization using Monte Carlo simulation, this exercise helped students comprehend the significance of process robustness in real-world industrial applications, where maintaining optimal conditions in the face of perturbations is crucial to ensure reliable product quality. By utilizing model tools to analyze robustness, students gained valuable insights into handling input variations.

The aforementioned three learning experiences helped students understand that an ideal model application is based on accurate model calibration.

Evaluation of Students' Performance

The final grade was determined based on the following factors: document formatting (15%), assignment completion (15%), rationality of model calibration (20%), rationality of model applications (20%), and time spent on completing all modeling tasks (30%). The first four criteria were assessed subjectively based on our experience, while the last criterion, time spent, was evaluated using a normal distribution calculated by taking the difference between the longest and shortest completion times. Results showed an average score of 91 for all students, with the lowest score being 80 and the highest score being 97.

Upon reanalyzing the assignments of students who scored close to the minimum of 80, it was observed that most of them failed to achieve satisfactory results due to the use of inappropriate optimization algorithms. Understanding these algorithms can be challenging for students without a strong mathematical background. Therefore, future practical teaching aimed at novice modelers may benefit from providing some background knowledge on algorithms. Separating practical teaching entirely from mathematical foundations made it difficult for students to effectively apply algorithms.

Furthermore, among the four students who had previous experience with chromatographic modeling tools, their average score was 93.75, which was higher than the overall average. This indicates that being familiar with chromatographic modeling tools positively influenced the students' performance.

Questionnaire Findings from Students

After the activity, we administered an online questionnaire among 63 students to evaluate the effectiveness of incorporating practical teaching of ion-exchange chromatography modeling tools into the traditional bioseparation engineering class. Out of the 54 valid responses received, two-thirds of the students expressed positive views on this innovative teaching approach, affirming its value for further implementation. The remaining one-third maintained a neutral stance, and no students opposed the introduction of this innovative method.

Through discussions with the students, we discovered that this innovative teaching method helped them better appreciate cutting-edge chromatography modeling knowledge, thus igniting their interest in learning about the chromatographic process. Furthermore, as a complementary approach, it strengthened their understanding of the fundamental chromatography principles acquired through traditional methods.

CONCLUSION

This paper presented an approach in practical teaching of modeling tools for ion-exchange chromatography with three

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parts: model introduction, model calibration through group learning using different calibration strategies, and model applications. This approach was integrated into the traditional bioseparation engineering curriculum as an activity, using the separation of monomer−dimer mixtures of monoclonal antibodies as an example. Results of competitive group learning and the Wilcoxon test revealed that the PbP method was more user-friendly than the Yamamoto method for novice modelers to obtain reasonable model parameters quickly. Then, students used the well-fitted model for process optimization, resulting in improved process performance. This helped students appreciate the critical role of time and material savings achieved through modeling tools. Additionally, students explored the effects of process parameters and material input variation on the chromatography process using the one-factor-at-a-time method and Monte Carlo simulation, respectively.

Through this practical teaching, students became familiar with chromatography modeling tools, overcoming the tedious formulaic descriptions of traditional courses and breathing life into textbook formulas, thereby strengthening their understanding of chromatography theory. The introduction of modeling tools in a bioseparation engineering course was innovative in igniting students' interest in emerging technologies. Results from students with diverse educational backgrounds showed that undergraduate students exhibited heightened interest in this emerging technology and completed modeling practices more efficiently.

Finally, the student questionnaire results revealed that over two-thirds of the students gave positive feedback on the activity. The use of chromatography modeling tools has vast potential in the biopharmaceutical industry. We will aim to expand the content of this well-designed practical course from academia to industry, providing training and guidance to industry personnel on using chromatography modeling tools. The training will transform the novice modelers into experienced modelers who can meet the changing demands of the modern biopharmaceutical industry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available at https://pubs.acs.org/doi/10.1021/acs.jchemed.3c00439.

Instructor's notes; student handout; descriptions of spreadsheets (PDF), (DOCX)

Spreadsheets of seven elution curves for model calibration (XLSX)

Gosilico project file (DSPX)

Spreadsheets for implementing the parameter-by-parameter method (XLSX)

Spreadsheets for collecting student modeling results (XLSX)

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Notes

The authors declare no competing financial interest.

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