





## Dynamic model-based control for process variations in ion-exchange chromatography

Ruo-Que Mao<sup>a</sup>, Yu-Cheng Chen<sup>b</sup>, Yu-Xin Liao<sup>a</sup>, Yu-Xiang Yang<sup>c</sup> , Shan-Jing Yao<sup>a</sup>, Dong-Qiang Lin<sup>a,\*</sup> 

<sup>a</sup> 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

<sup>b</sup> Marine Biological Manufacturing Center of Fuzhou Institute of Oceanography, Fuzhou University, Fuzhou 350108, China

<sup>c</sup> Department of Chemical Engineering, University of Melbourne, Victoria 3010, Australia

### ARTICLE INFO

#### Keywords:

Ion exchange chromatography  
Mechanistic model  
Model predictive control  
Process optimization  
Bioseparation

### ABSTRACT

The capability of smart manufacturing to enable predictive and autonomous decision-making under uncertainty is highly valuable to ion-exchange chromatography (IEC), a critical purification step that is sensitive to variations in sample composition and loading density. However, conventional IEC operation relies on predefined elution conditions, including fixed elution gradient and collection window, which limits its adaptability to process variations. To address this limitation, a model-based control system was developed for the dynamic and autonomous optimization of IEC under process variations. The system incorporated the mechanistic models that combined equilibrium dispersive model and steric mass action model to quantitatively predict protein elution behavior. By integrating communication technologies, the model predictions were used to automatically determine and implement the optimal elution gradient and collection window, enabling model-based decision-making. The experimental validation demonstrated that the model-based control system consistently achieved purity above 96.0% and yield exceeding 88.0%. These results indicate that both product quality and process performance could be maintained despite process variability. Overall, the proposed model-based control system enabled the dynamic and simultaneous adjustment of elution gradient and collection window, transforming IEC operation from predefined conditions to a predictive and adaptive control approach, thereby enhancing process robustness and operational flexibility.

### 1. Introduction

Smart manufacturing is widely recognized as a key driver of industrial transformation and advancement [1–3]. By integrating advanced sensors, modeling, simulation, and data analytics, it enhances process understanding, as well as decision-making and operational planning [4, 5]. These predictive and autonomous capabilities are particularly important in the biopharmaceutical industry, which faces increasing financial pressure due to market competition from biosimilars [6] and high cost of goods [7]. Consequently, there is a growing demand for improved cost-effectiveness, enhanced product quality, and higher process flexibility in critical biomanufacturing steps.

Ion-exchange chromatography (IEC) is a critical and well-established unit operation in biopharmaceutical processes, commonly employed in polishing steps to achieve stringent product purity requirements [8–10].

However, conventional IEC process operation depends largely on empirical experience, typically based on a one-factor-at-a-time (OFAT) approach to define operating conditions [11]. Such approaches necessitate extensive manual experimentation, result in inefficient use of resources, and may not fully account for potential interactions among process variables [12].

In response to these challenges, mechanistic models have attracted increasing attention as tools for systematic characterization and improved understanding of chromatography processes. Such models describe the separation of the target protein and impurities across stationary and mobile phases, accounting for both mass transfer (convection, axial dispersion, and diffusion) and adsorption behavior [13–15]. Mechanistic models have been widely applied to support process development and optimization, significantly reducing experimental effort and accelerating process design [16–22]. However, once optimal

\* Corresponding author at: College of Chemical and Biological Engineering, Zhejiang University, Hangzhou 310058, China.

E-mail address: [lindq@zju.edu.cn](mailto:lindq@zju.edu.cn) (D.-Q. Lin).

<https://doi.org/10.1016/j.chroma.2026.467103>

Received 15 April 2026; Received in revised form 13 May 2026; Accepted 14 May 2026

Available online 15 May 2026

0021-9673/© 2026 Elsevier B.V. All rights reserved, including those for text and data mining, AI training, and similar technologies.