Chromatographic Processes

Addressing all aspects of the design, modeling, and simulation of chromatographic processes, this result-oriented primer provides a practical guide to all the necessary approaches, methodologies, and tools.

Beginning with key definitions and concepts, it builds up from the simplest to the most complex situations, including multicomponent systems, non-uniform velocity profiles, bed instability, particle size distributions, and the influence of complex environments on chromatographic process design. In addition to covering classical approaches, it introduces efficient tools for investigating chromatographic processes, such as the "Russian-Lego" approach for linear systems, phenomenological models, and specific shortcuts for deriving the key properties of industrial processes.

With an emphasis on real-world problems and applications, step-by-step modeling design guidelines, and detailed exercises for self-assessment, this is a must-have guide for practitioners and researchers working in chemical, biochemical, food, and pharmaceutical engineering.

Roger-Marc Nicoud is the founder and former CEO of Novasep, which has installed over 2000 chromatographic units worldwide and pioneered the use of large-scale continuous chromatographic processes in the life science industry. He is President of École Nationale Supérieure des Industries Chimiques (ENSIC), and in 2014, founded YpsoFacto (www.ypsofacto.com).

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Modeling, Simulation, and Design

ROGER-MARC NICOUD

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Preface and acknowledgments

No three inventions have had greater impact on the working day of the physical scientist than the computer, the photocopier and the chromatograph.
Friedrich Helfferich, 1986

The dramatic increase in purification needs, from the development to the production stage, especially in the pharmaceutical and biopharmaceutical industries, has led preparative chromatography to become a widely used technology. There are now so many companies, teams and individuals using or developing preparative chromatographic processes that a real chromatographic world has appeared during the last decades.

Experience shows that very diverse people are living in the chromatographic world. Some of them come from the "Chemists" planet and they speak about polarity, adsorbent deactivation or resolution. The ones from the "Biochemists" planet speak about protein denaturation, isoelectric points or viral contamination. Others come from the "Chemical Engineers" planet and speak about mass transfer, dispersion coefficients and adsorption isotherms. Those from the "Pharmacists" planet speak about contamination or good manufacturing practices. One can even find people from the "Mathematicians" planet, speaking about Riemann invariants or Laplace transforms. Obviously, since all of these people use their own language, the chromatographic world may sound very dissonant, not propitious for discussion.

My experience, skills and passion are certainly on the chemical engineering side. The chemical engineering methodology, "La voie Royale" in the terminology of Jacques Villermaux, sounds like a rational way to approach complex problems. My confidence in the ability of this approach to efficiently design chromatographic processes is at the origin of my decision to create Novasep. Twenty years later, I know how fruitful the approach is, but I also know how hard it is to explain and to diffuse it. Rational chemical engineering approaches are too seldom used in the industry, and the emergence of Quality by Design (QbD) and associated Design of Experiments (DoE) approaches, encouraged by the authorities and embraced by the industry, sounds too often like a refusal to understand the physics of chromatography.

I decided to write this book in order to present a chemical engineering approach in a comprehensive manner, and to help people coming from different origins to appreciate what can be expected from this approach. The content is not exhaustive, as for instance chromatographic media are not presented, and perhaps not even objective: only

information considered useful according to my experience has been included. I readily apologize if important contributions are not mentioned; this would simply be a measure of my ignorance.

This book has been written in order to show how concepts may help in solving practical problems ("the real world"), and how practical problems may give some very interesting research subjects for which new concepts are probably required. Instead of giving recipes, I propose a methodology that will, I believe, help the reader to solve even the most difficult problems. I know that some chromatographers may find some parts difficult because of the mathematics involved. I have done my best to illustrate any part that could be of specific difficulty, but I believe that this complexity is the price for access to the methodology. If somebody wants to learn guitar, he has to accept that the instrument has six chords, even if initially this number seems way too high.

The first chapters of the book are devoted to understanding and modeling chromatographic processes. Starting with simple models of linear chromatography with incompressible fluids, various simplifying assumptions are progressively relaxed, and models of increasing complexity are proposed for describing, with the required degree of precision, the thermodynamic, hydrodynamic and mass-transfer processes that determine a chromatogram's shape.

The theoretical concepts presented in the first chapters are then used for selecting and optimizing different chromatographic processes. The theoretical models are used as tools to predict the behavior of chromatographic systems in unexplored regions, assuming that an optimization criterion is known for selecting the most appropriate system.

The approach presented in this book is the result of 30 years of involvement in chromatography, starting with research work on ion exchange initiated in 1984 in the Laboratoire des Sciences du Génie Chimique, Nancy. Professor J. Villermaux was the Director of the Laboratory, and Dr. D. Schweich my research director. I will never be able to express how these first years, and the opportunity to benefit from the exceptional scientific skills of Professor Villermaux and Dr. Schweich, have been critical for my entire career.

The work continued at Separex, and my early cooperation with Professor M. Perrut has been instrumental in making things happen and building the confidence that concepts will eventually lead to design, design to reality.

Many ideas presented in this book have been developed, tested or improved during more than two decades with my coworkers, and especially P. Adam, J. Blehaut, Dr. F. Charton, Dr. J. Y. Clavier, Dr. H. Colin, Dr. F. Denet, Dr. W. Hauck, Dr. M. Holzer, Dr. O. Ludemann-Hombourger and Dr. E. Valery. Some partners from academia, with whom I co-authored scientific publications or co-directed theses, also played important roles, and the names of Dr. M. Bailly, Professor M. Morbidelli, Professor M. Mazzotti, Professor A.E. Rodrigues and Professor A. Seidel-Morgenstern immediately cross my mind. More recently, I had some discussions with Professor M. Kaspereit on a preliminary version of the book, and he then contributed to improving the presentation of the single-solute equilibrium model; Professor J.P. Mota and Professor A.E. Rodrigues agreed to read and comment on the manuscript; D. Pfister was brave enough to perform a

final detailed check. Even prior to the creation of Novasep, when using counter-current chromatography for producing active pharmaceutical molecules was no more than a dream, I benefited from the unconditional support of Professor Kinkel, at that time head of the preparative chromatography laboratory at Merck (Darmstadt). I would like to express to all of them my sincere gratitude.

As a consequence of these historical cooperations, I will normally use the first person plural for presenting models and results, and the first person singular for expressing an opinion.

The roots of this book can probably be found in the early 1990s, when I received support from the European Union program COMETT for producing materials aimed at teaching a methodology for designing chromatographic processes. I then, from time to time, worked with Dr. Michel Bailly, in order to extend the initial material, and to propose a book. My professional duties did not allow me to allocate the time required for moving forward efficiently, so the writing was put on hold for many years. When I took a break from operational management, my first desire was to complete what was initiated so long ago. In writing this book, organizing things and reading recent contributions, I realized that I could have made better use of some interesting concepts and tools. These are mentioned, although briefly, in order to share some possible directions with those who are now in charge of developing the existing knowledge and methods.

In order to produce a document of the highest possible quality, I asked Dr. Daniel Schweich to check and critically review the content. He accepted immediately, and I have to admit that I feel some guilt because I did not realize how big this task was going to be. I would like to express to him my gratitude for having taken on the challenge. This book owes him a lot.

Roger-Marc NICOUD