INTEGRATED GRADUATE AND CONTINUING EDUCATION IN PROTEIN CHROMATOGRAPHY

for Bioprocess Development and Scale-up

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Chromatography has become an essential unit operation in the production of biopharmaceuticals. This method facilitates the processing of the complex mixtures encountered in this industry using readily available stationary phases and equipment suitable for large-scale sanitary operation. Moreover, its practice as a process purification tool is recognized by regulatory agencies so that chromatography is an integral part of essentially all licensed biopharmaceutical processes. Figure 1 shows typical downstream process (DSP) flow diagrams for soluble recombinant proteins expressed in bacterial systems (*e.g., E. coli*) and for monoclonal antibodies expressed in mammalian cells. In both cases, chromatography plays a dominant role in the three major tasks of:

(a) ***Capture*** *– devoted primarily to concentrating and separating the protein product from water and product-unrelated impurities;*

(b) ***Purification*** *– focused on the separation of major product-related impurities, including modified protein forms; and*

(c) ***Polishing*** *– focused on the removal of trace contaminants and adventitious agents.*

Since the process characteristics, the optimum stationary phase properties, and the design requirements are very different for each of these operations, an in-depth understanding of how process variables affect performance, efficiency, and reliability is desirable and is increasingly being sought by regulatory agencies. As a result, chemists, engineers, and life scientists working in this field need to become familiar with the theory and practice of process chromatography.

Process scale economics also plays a major role. Figure 2 shows the relative contributions of upstream and downstream processing material costs for recombinant proteins produced in bacterial systems and for monoclonal antibodies produced by mammalian cell culture. Increasing product titers obtained from improved genetic engineering and cell cultivation practices, nowadays approaching the 5 to 10 g/L levels, create new technological challenges and capacity bottlenecks—increasingly shifting the costs from upstream to downstream.[2-4] The evolving regulatory environment for

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Alois Jungbauer *is the head of protein technology and downstream processing at the Department of Biotechnology of the University of Natural Resources and Life Sciences in Vienna (Austria). For more than 20 years, Professor Jungbauer has worked in biochemical engineering, with a focus on biosparation, where he has published widely and holds 15 patents. For more than 10 years, he has organized a biennial professional course in protein chromatography focused on mass transfer, dispersion, and scale-up.*

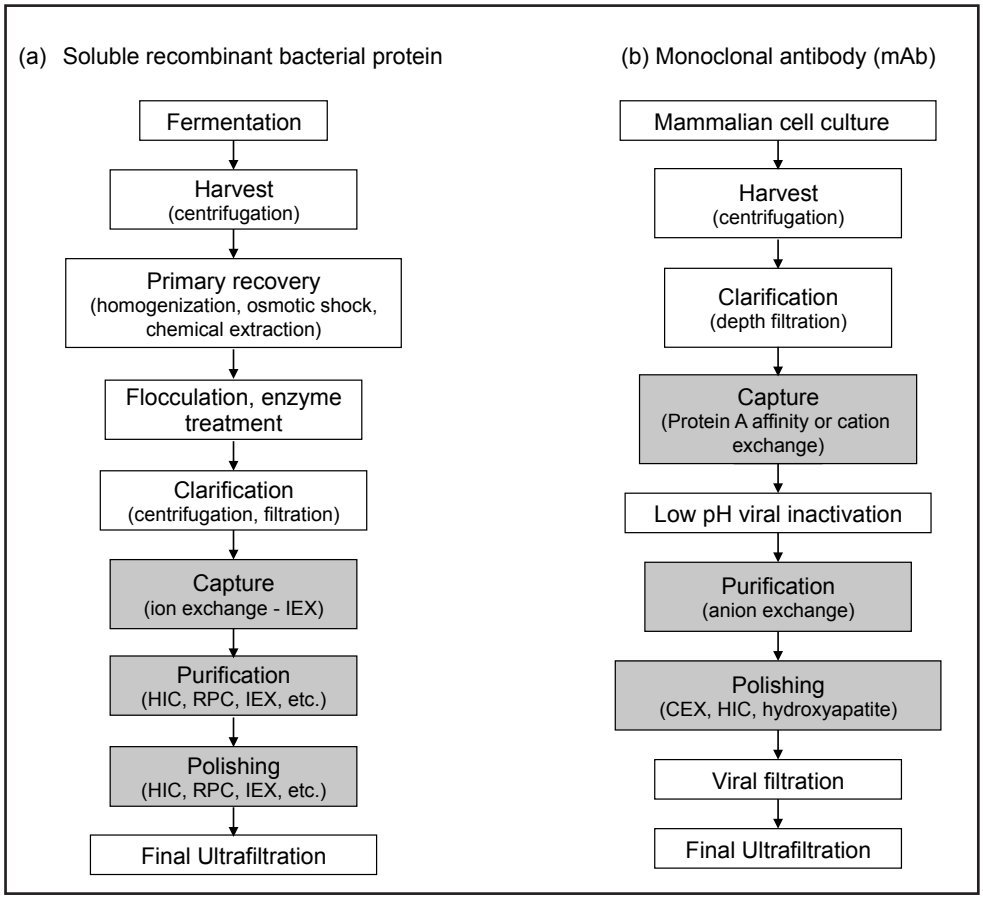
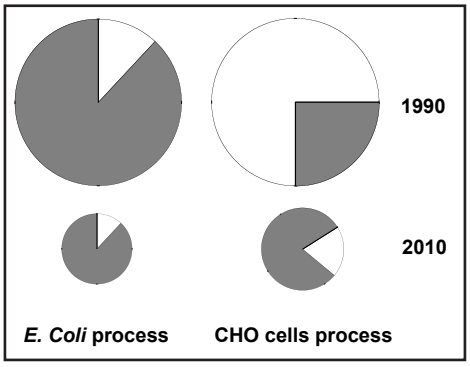


Figure 1 (left). *Downstream processing schemes for a soluble protein expressed in a bacterial fermentation (a) and for a monoclonal antibody expressed in mammalian cells (b). Chromatography steps are shown in gray-shaded boxes. Courtesy of Alan Hunter, MedImmune.*

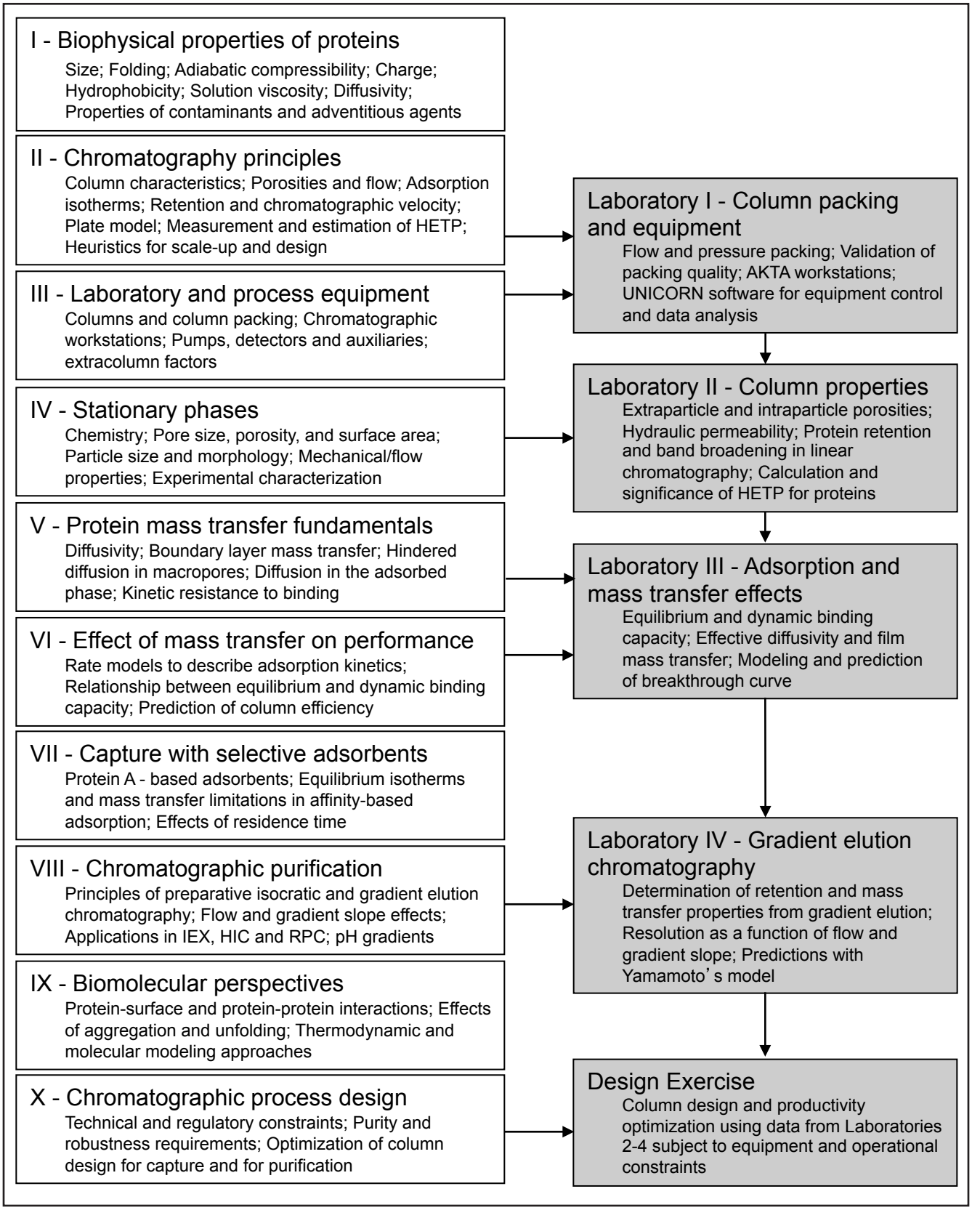
Figure 2 (below). *Typical distribution of production costs for biopharmecauticals produced in* E. coli *and Chinese Hamster Ovary (CHO) cells in the nineties according to Datar, et. al.,[1] (top), and in 2010 (bottom); upstream (fermentation) is in white and downstream is in gray. Note that increasing monoclonal antibody titers obtained from mammalian cell cultivation, now easily approaching 5 to 10 g/L, and tightening purity requirements increasingly shift the costs from upstream to downstream processing. The total areas of the pie charts indicate the relative magnitude of the total processing cost.*



biopharmaceuticals and the introduction of so-called "biosimilars" will also offer new opportunities for improving production and reducing costs. Unlike many small molecule drugs, protein-based therapeutics are characterized by extreme molecular complexity. As a result, current U.S. FDA regulations (<http://www.fda.gov/cber/>) essentially define biological drugs by the process used to produce them. As a consequence, process changes after product licensing have been extremely difficult to implement. Recent emphasis on "quality by design" (QbD), however, is gradually moving the regulatory framework toward a more rational approach. QbD refers to the achievement of certain predictable quality with desired and predetermined specifications based on a fundamental understanding of the process. Biosimilars, defined as subsequent versions of approved biological drugs produced by a follow-on manufacturer generally through a different process, also create opportunities for process engineering since they tend to separate product qualities from the exact process used to produce them.

While, in general, the theory and practice of liquid chromatography is well established for small molecule separations (*e.g.*, see References 5-9), the design and scale-up of chromatography units for biopharmaceutical purification remain largely empirical. Thus, optimum designs often remain elusive. On one hand, engineers, while possessing a strong foundation in transport phenomena and unit operations, often have a limited understanding of biomolecular properties. On the other, biochemists and biologists often have limited understanding of the key scale-up relationships and models needed for optimum design.

In an effort to address this dichotomy, in 2000 we started a new short course at BOKU in Vienna, Austria, with the principal aim of merging the theory and practice of biochromatography


I - Biophysical properties of proteins
Size; Folding; Adiabatic compressibility; Charge; Hydrophobicity; Solution viscosity; Diffusivity; Properties of contaminants and adventitious agents
II - Chromatography principles
Column characteristics; Porosities and flow; Adsorption isotherms; Retention and chromatographic velocity; Plate model; Measurement and estimation of HETP; Heuristics for scale-up and design
III - Laboratory and process equipment
Columns and column packing; Chromatographic workstations; Pumps, detectors and auxiliaries; extracolumn factors
IV - Stationary phases
Chemistry; Pore size, porosity, and surface area; Particle size and morphology; Mechanical/flow properties; Experimental characterization
V - Protein mass transfer fundamentals
Diffusivity; Boundary layer mass transfer; Hindered diffusion in macropores; Diffusion in the adsorbed phase; Kinetic resistance to binding
VI - Effect of mass transfer on performance
Rate models to describe adsorption kinetics; Relationship between equilibrium and dynamic binding capacity; Prediction of column efficiency
VII - Capture with selective adsorbents
Protein A - based adsorbents; Equilibrium isotherms and mass transfer limitations in affinity-based adsorption; Effects of residence time
VIII - Chromatographic purification
Principles of preparative isocratic and gradient elution chromatography; Flow and gradient slope effects; Applications in IEX, HIC and RPC; pH gradients
IX - Biomolecular perspectives
Protein-surface and protein-protein interactions; Effects of aggregation and unfolding; Thermodynamic and molecular modeling approaches
X - Chromatographic process design
Technical and regulatory constraints; Purity and robustness requirements; Optimization of column design for capture and for purification
Laboratory I - Column packing and equipment
Flow and pressure packing; Validation of packing quality; AKTA workstations; UNICORN software for equipment control and data analysis
Laboratory II - Column properties
Extraparticle and intraparticle porosities; Hydraulic permeability; Protein retention and band broadening in linear chromatography; Calculation and significance of HETP for proteins
Laboratory III - Adsorption and mass transfer effects
Equilibrium and dynamic binding capacity; Effective diffusivity and film mass transfer; Modeling and prediction of breakthrough curve
Laboratory IV - Gradient elution chromatography
Determination of retention and mass transfer properties from gradient elution; Resolution as a function of flow and gradient slope; Predictions with Yamamoto's model
Design Exercise
Column design and productivity optimization using data from Laboratories 2-4 subject to equipment and operational constraints

to achieve optimum design and scale-up of process units. Our goal was to help educate engineers who understand the biophysical properties of proteins and other bio-macromolecules and can implement this understanding in the bioprocess setting; and life scientists who understand transport phenomena and engineering models and who can apply these tools to the design of process units. The course has been held annually both in Vienna and at the University of Virginia, in Charlottesville, Virginia, and has both theoretical and practical, hands-on components. In the lectures, the participants learn the fundamentals of protein production—the structural and biophysical properties of proteins and the varied nature of their contaminants; the theory of chromatography; the properties of stationary phases; how to describe the equilibrium and kinetic factors that govern process performance; and how to achieve a proper balance of separation efficiency and productivity. In the laboratory, they learn to pack columns that are useful as scale-down models; to plan experiments to identify critical parameters; and to use advanced chromatography workstations to measure the critical physiochemical properties needed to model retention and band broadening in different types of chromatographic operations. Ultimately, the participants complete a design exercise, in which they are asked to design an optimized column on the basis of the laboratory measurements and theories learned during the course.

It should be noted that the main value of this course is not in *de novo* process development—rather, it mainly focuses on the optimal design and scale-up of columns for a process for which the steps have already been defined. For example, we consider the case of a monoclonal antibody process produced by mammalian cell culture for which a platform purification structure has been defined according to Figure 1. Monoclonal antibodies are important biopharmaceuticals with many applications in the treatment of serious diseases and with market volume in the tens of billions of dollars per year. The bottleneck in their manufacture is often the capture step, which requires large columns (because of the limited binding capacity) and long times (because of severe mass transfer limitation). Our course offers the tools for optimally designing columns that can perform this task at maximum productivity with available stationary phases. Nevertheless, understanding these design concepts also aids the scientist who is involved in early process development to identify process steps that are scalable and can be efficiently translated from the laboratory to the manufacturing suite.

Figure 3 (facing page). *Course content and organization: unshaded boxes show lectures while shaded boxes indicate laboratories and team activities.*

COURSE CONTENT AND ORGANIZATION

Several approaches to teaching bioseparations, including computer simulations of adsorption and chromatography,[10] illustrating chromatography with colorful model proteins,[11] and chemical engineering laboratory courses covering multiple bioseparation operations,[12,13] have been presented. Our approach is substantially different both in scope and delivery, however. It consists of an intensive short course comprising 10 1.5-hour lectures, four laboratories, and a design exercise that integrates academic and industrial participants. The course program has evolved over the years, but the typical plan and main topics are shown in Figure 3. The first lecture unit covers the biophysical properties of proteins and related molecules. We emphasize their complexity—defining levels of structure, folding characteristics, post-translational modifications, charge, and hydrophobicity as well as solution properties including solubility, viscosity, and diffusivity. While life scientists are generally familiar with these concepts, they have typically not thought about them in relation to their effects on process performance; many of the participants with engineering backgrounds have only a very superficial appreciation of their molecular complexity. Covering this material, albeit in a necessarily succinct way, brings the heterogeneous set of participants to common ground. The second lecture unit introduces key concepts that form the basis for understanding how chromatographic columns work and how they can be scaled-up. Rather than dealing with each type of chromatography separately, we emphasize their common basis, treating chromatography as a unit operation. The empirical plate model is introduced at this stage as a simple tool for design and scale-up. We note that while effective when used in combination with experiments, this simple model does not permit a physically realistic assessment of the effects of mass transfer resistances, which tend to be dominant in these applications.

The next two lecture units (III and IV) cover laboratory and process columns and equipment and stationary phases. After a general introduction of the desirable characteristics of these essential "hardware" components, we provide many practical examples of equipment and materials available on the market. Chromatography media have often been chosen either based on what "worked before" or on manufacturers' recommendation. We emphasize that while these approaches are valuable, a better choice can often be made with a fundamental understanding of chemical and physical characteristics in relation to the particular separation task at hand. The range of materials and column technologies available is expanding rapidly. Thus, the importance of understanding the basics is growing in order to be able to navigate an increasingly complex field.

Lecture units V and VI cover the fundamentals of protein mass transfer and its effects on chromatographic column performance. Because of the large molecular size and the often high solution viscosity and low operating temperature, diffusional mass transfer in the stationary phase is often the controlling band-broadening factor in protein chromatography. We describe different possible mass transfer mechanisms both theoretically and using images of proteins diffusing in chromatography particles obtained by confocal laser scanning microscopy (CLSM) and other microscopic techniques. We then illustrate how mass transfer resistances accelerate breakthrough, reduce the attainable binding capacity, and broaden chromatographic peaks leading to lower resolution and/or yield of the purified product. The key scale-up concept introduced at this stage is that for the mass transfer controlled conditions encountered in these systems, the critical scale-up parameter is the number of transfer units defined as $n = 60(1-\varepsilon)D_e L/ud_p^2$ where ε is the column extraparticle porosity, D_e the effective pore diffusivity, L the column length, u the flow velocity, and d_p the particle diameter. We show that since column pressure depends on Lu/d_p^2, the column aspect ratio (L/d_{column}) can be changed while keeping n constant to allow the design of columns that retain the same dynamic binding capacity and ability to resolve mixtures, while meeting specified pressure limits. A good question posited at this stage is what pore size should be chosen to handle the capture of a large biomolecule or its separation from related impurities. To answer this question we discuss hindered diffusion theory and show that, as a general rule, the pore size needs to be five to 10 times the size of the protein in order to avoid extreme diffusional hindrance and exceedingly slow transport. For a monoclonal antibody, whose diameter is on the order of 10 nm, this leads to pore sizes between 50 and 100 nm, which are in fact used in practice.

Lecture units VII and VIII elaborate on capture with selective adsorbents and separation of product-related impurities. The main example of selective capture is Protein A-based adsorbents, which selectively bind immunoglobulin and are used extensively in monoclonal antibody manufacturing processes. Special attention is devoted to gradient elution as a tool for the separation of closely related impurities. Protein binding is generally very sensitive to the exact composition of the mobile phase, making isocratic chromatography difficult to implement at the industrial scale because of limited robustness. Gradient elution, where the mobile phase composition is gradually ramped from conditions leading to strong retention to conditions where binding is weak, provides a more robust and controllable process, although some complications are introduced. In this context we explain how protein retention and resolution vary with gradient slope and how the gradient slope affects the mobile phase composition at which elution of the separated products occurs. We introduce the method of Yamamoto discussed in Reference 9 to obtain retention and transport parameters from gradient elution experiments as a practical tool useful to generate useful scale-up parameters.

Lecture unit IX refocuses the group's attention on biomolecular properties. Now that the participants are familiar with how chromatography is implemented at the process scale and what parameters affect its performance, we address various factors that contribute to deviations from the theoretical behavior, including protein-protein and protein-surface interactions that can lead to aggregation and/or unfolding. Several examples are discussed primarily in the context of hydrophobic chromatography including a discussion of modern techniques such as hydrogen-deuterium exchange with mass spectrometry to detect unfolding on column and in solution.

The final lecture unit, X, is designed to bring most concepts together by illustrating how to design maximum-productivity columns for capture and for resolution. We provide an overview of technical and economic constraints, but we emphasize designs that maximize productivity since the cost of the stationary phase and column hardware are often dominant. Thus, maximizing productivity often yields designs that are close to the true economic optimum. Column pressure is frequently the chief constraint, sometimes limited to just a few bars for large-scale bio-process columns. We thus show how to design columns that meet these low-pressure constraints for both rigid stationary phases and for compressible media.

The lecture material, developed over several years, is now available in our recently published book.[14] Other references are used extensively in our course.[15-17] The lectures are presented in PowerPoint format and include a substantial number of spreadsheet-based tools, which implement quantitative relationships introduced in the lectures, and provide valuable demonstrations. For example, one of the spreadsheet tools provides a live simulation of protein diffusion and adsorption in a spherical particle allowing the user to experiment with the effects of particle size, protein concentration, diffusivity, and isotherm shape. Another spreadsheet tool allows visualization of the adsorption front propagating through a column during a capture step. Simulations are presented for conditions where the adsorption isotherm is non-linear, since these conditions are more frequently encountered in process scale application of chromatography at high protein loads. An example is shown in Figure 4. The spreadsheet simulates the propagation of an adsorption front through a column and is used to illustrate the rapid approach to a "constant pattern"[9] when the adsorption isotherm is non-linear and favorable. For short times, the profiles are exponentially decaying functions. For

longer times, however, the profiles acquire the characteristic S-shape, which is retained unchanged as the front continues to propagate toward the column exit and breakthrough occurs. The spreadsheet is also used to simulate various effects such as that of residence time (L/u), feed and initial concentrations, particle size, and effective diffusivity. The last two parameters, of course, are affected by the choice of the stationary phase, so that basic mass transfer theory can be put in a practical context recognizable by both life scientists and engineers. Since instantaneous graphical displays are included, these tools provide a familiar environment to explain key relationships in a manner accessible even by those who lack in-depth mathematical knowledge. The course participants are provided with printed notes in binders as well as electronic versions. Model simulation spreadsheets used in the course are available from the authors upon request.

The laboratories are based on experiments with actual proteins (molecular masses between 12 and 150 kDa) using

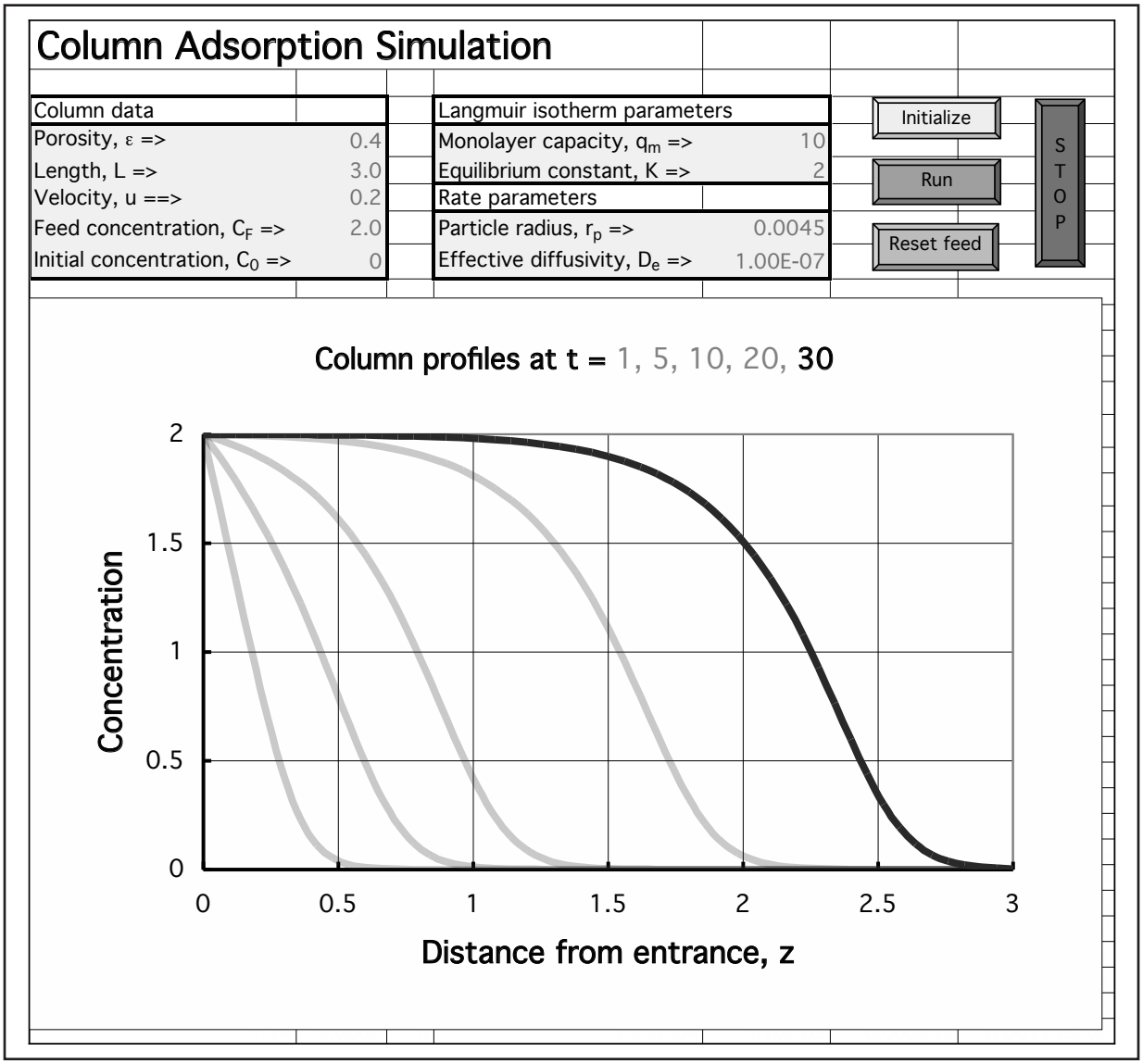


Figure 4. *Screenshot of sample spreadsheet used to simulate the propagation of an adsorption front in a capture column. The simulated profiles, obtained with a favorable Langmuir-type binding isotherm, demonstrate the rapid approach to a constant pattern that retains its shape as breakthrough occurs. Conditions simulated are typical for protein chromatography. Dispersion is controlled by intraparticle diffusion.*

state-of-the-art AKTA Explorer 10 and 100 chromatographic workstations from GE Healthcare (Piscataway, NJ, USA). These units integrate sophisticated pumps, sample injectors, column switching valves, and multiple detectors with powerful control and data acquisition software (UNICORN). The flow diagram of the AKTA system used and a photograph are shown in Figure 5. The four laboratory units shown in Figure 3 are intercalated with the lecture units so that the various concepts introduced in the lectures are tested in the laboratory immediately after they are presented.

The course is conducted over a six-day period. On the first day, we survey the participants to assess their level of experience with protein chromatography, engineering vs. life science backgrounds, laboratory vs. manufacturing job function, and nationality. This information is used to create six-person teams where each member can contribute different skills. Since the biotechnology industry is highly multidisciplinary, the participants have come from an extremely broad range of educational background and experience, which provides an excellent environment for shared learning opportunities. Thus, each team typically comprises chemical engineers, life scientists, experienced chromatographers, participants who are at their first encounter with protein chromatography, and even product managers and marketing specialists. Each team is assigned a graduate student from our groups as a tutor and assistant. For each lab, the tutors go over the key concepts covered in

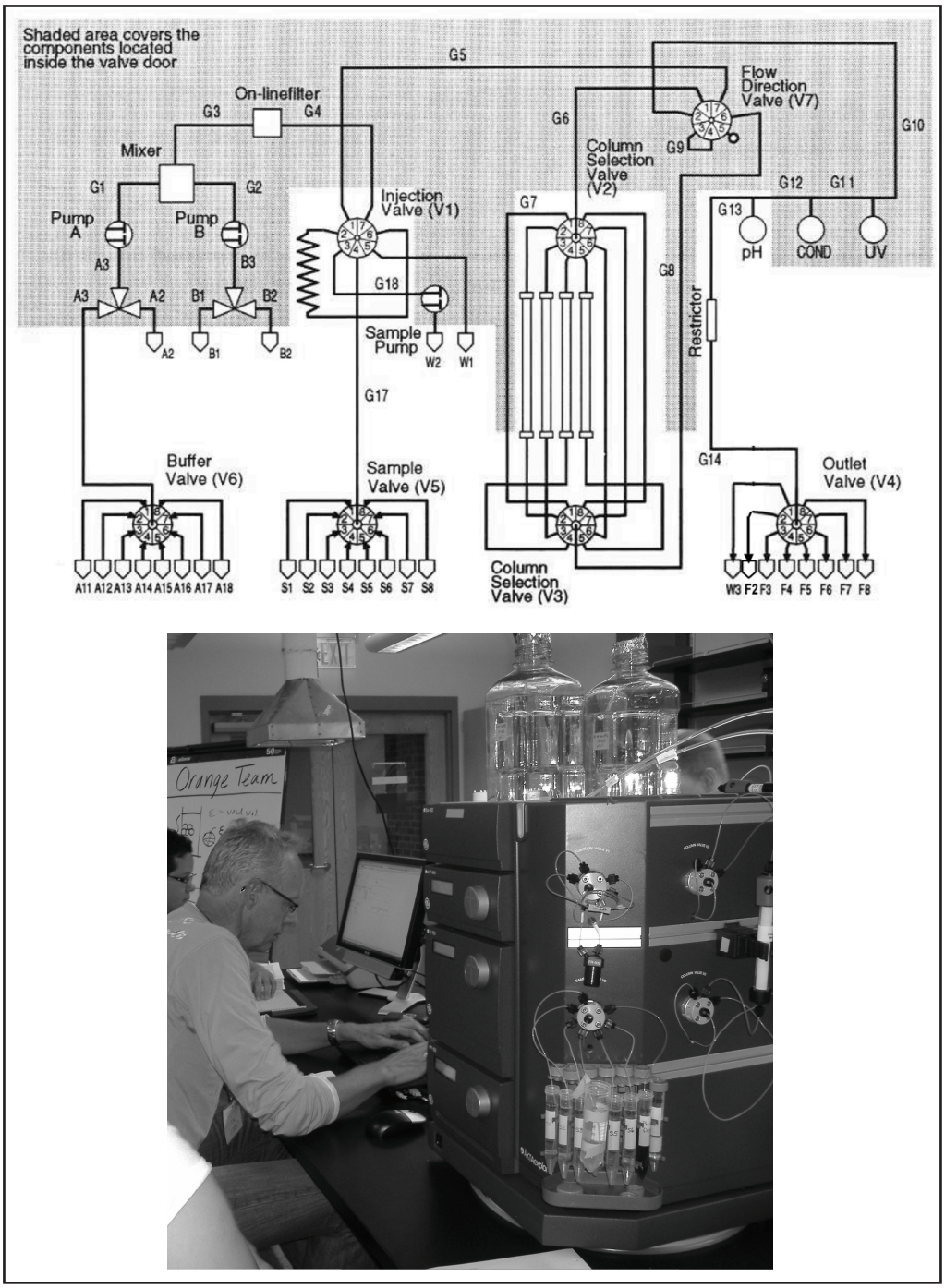


Figure 5. *Flow diagram (top) and photograph (bottom) of AKTA Explorer 10 unit from GE Healthcare used in the experimental part of the course. A unit is assigned to each team of six participants.*

the lectures that are relevant to the lab at hand, explain the goals of the experiments, and guide each team through the setup of experimental runs. Some runs are executed quickly and the results are subjected to a preliminary analysis. The "scouting" feature of UNICORN is then used to explore a broad range of conditions overnight, generating a substantial number of runs. The next day each team analyzes the data in detail. We emphasize manual, hand calculations (that enhance understanding) as well as spreadsheet tools (that allow the analysis of large amounts of data). Each team is given different proteins with varying molecular properties and the two different stationary phases SP-Sepharose-FF and Source 30S (both from GE Healthcare) having different particle sizes (90 and 30 μm, respectively), particle size distributions (broad and uniform, respectively), pore sizes (30 and 200 nm, respectively), porosities (85 and 50%, respectively), and mechanical strengths (soft and rigid, respectively), packed in columns of different diameters and lengths (0.5-1 cm and 3-10 cm, respectively). For each, the teams derive critical properties (porosities, hydraulic permeability, binding constants and capacities, effective diffusivities) that are needed to understand the relative efficacy for different applications and for the design and scale-up of production scale columns. After each lab analysis period, each team presents the results to the entire group, which is followed by group discussion of what worked according to theory and what did not. We then continue with the next lecture in preparation for the subsequent lab.

Throughout the week, the participants are asked in turn to help fill out a large table summarizing the results of the experiments, the main features of the different stationary phases, how the protein molecular properties affect the results, and the lessons learned about the effects of critical operating parameters. At the end, based on the information compiled from the four laboratories, the participants make predictions of the separation performance of a third hypothetical stationary phase that combines the smaller pore size and larger porosity of SP-Sepharose-FF with the smaller particle size of Source 30S and for proteins with physiochemical properties that differ from those studied experimentally. In our experience, at the end the course, the participants get it right!

TABLE 1
Distribution of Course Participants

Participants	Number
Participants from industry	250
Participants from universities and public research institutions	81
Categories	**Number**
Companies	51
Biotech & pharma	35
Design & contract manufacturing	5
Media & equipment suppliers	11
Universities and public research institutions	16
Nationalities	16

The design exercise held on the last day of the course provides a further opportunity to strengthen conceptual and practical understanding of the factors that need to be considered to arrive at optimized designs that meet specified constraints. This is done again in a team setting with assistance from the tutors. An example problem is as follows:

> *You are assigned the task of scaling-up a cation-exchange capture step with SP-Sepharose-FF for the capture of the protein you tested in the laboratory. The feed will be in 2000 L batches of clarified solution containing 2 g/L of your protein plus several minor impurities including proteins that are expected to have a pI around 5, endotoxin, DNA, carbohydrates, amino acids, and other trace components. The feed viscosity is 1.5 mPas. The proposed capture step will serve mainly to capture and concentrate the protein, although separation from the impurities is desirable. A 45-cm diameter column with adjustable bed height (10-60 cm) and a pressure rating of 3 bar is available. Your job is to determine if the available hardware is suitable and the processing time based on your lab-scale experiments.*

Since the design is constrained by available column hardware and maximum protein concentration, the teams have to be creative and discover that greater productivity can be obtained by running a single shorter column for several cycles rather than a single cycle in a larger one. Among other things, the example demonstrates how optimized designs can help remove the downstream processing bottleneck created by the high fermentation titers and greater product demands that have arisen in recent years.

ASSESSMENT

So far the course has been held seven times at BOKU and seven times at UVa. The authors have served as the organizers and principal lecturers in both venues although a few other faculty members have also participated. We have strictly limited the number of participants to no more that 24 for each course and thus far we have had a total of 331 participants, 167 at UVa and 164 at BOKU. A breakdown of the participants' backgrounds is given in Table 1. The international aspect is an important part of the experience since it also provides a view of the different industrial environments and regulatory structures in the United States, Europe, and other countries.

This is also true for the tutors, since each year we exchange students between the BOKU and UVa groups.

The course is assessed through written course evaluations shown in Figure 6. The average overall course rating during the last five years has been 3.839 on a scale of 0-4, with 4 being excellent. Virtually 100% of the participants have indicated on the evaluation form that they would recommend the course to a colleague or associate. Indeed, the course has been oversubscribed for the last five years and for each offering we have had a long waiting list.

We feel that the course provides the following benefits:

For the industrial participants:

- *An introduction to the fundamental underpinnings of protein chromatography and to advanced laboratory equipment and techniques for process development and scale-up;*
- *The tools to understand and troubleshoot actual bio-manufacturing processes;*
- *Retraining of industrial separation scientists who have experience with small molecules but who are now challenged by large biomolecules;*
- *The background needed to implement Quality-by-Design (QbD), which is a critical component of the FDA's efforts to improve the drug approval process, reduce costs, and improve quality;*
- *Networking opportunities with other companies; and*
- *Motivation to pursue advanced studies by being immersed in thriving academic environments.*

For the academic participants:

- *An exposure to practical laboratory and manufacturing aspects of the biopharmaceutical industry;*
- *An understanding of the regulatory, economic, technological, and operational constraints affecting downstream process design and operation;*
- *The value of fundamentals in solving practical design problems;*
- *An exposure to teamwork in a highly multidisciplinary setting not commonly found in purely academic courses;*
- *An opportunity to learn how to present research results to a broad audience;*
- *Motivation to pursue careers in the biopharmaceutical industry; and*
- *Opportunities to network with industrial biotech.*

Finally, for the graduate students involved as tutors:

- *The opportunity to learn by teaching a multidisciplinary team;*
- *The development of team leadership skills;*

Lectures	Excellent	Good	Fair	Poor	N/A
Technical content	☐	☐	☐	☐	☐
Clarity of presentations	☐	☐	☐	☐	☐
Clarity of notes	☐	☐	☐	☐	☐
Knowledge of instructors	☐	☐	☐	☐	☐
Response to in-class questions	☐	☐	☐	☐	☐
Overall lectures rating	☐	☐	☐	☐	☐

Laboratory sessions	Excellent	Good	Fair	Poor	N/A
Technical content	☐	☐	☐	☐	☐
Equipment	☐	☐	☐	☐	☐
Clarity of lab objectives and plans	☐	☐	☐	☐	☐
Clarity of data analysis tools	☐	☐	☐	☐	☐
Quality of tutor support	☐	☐	☐	☐	☐
Overall laboratories rating	☐	☐	☐	☐	☐

Organization	Excellent	Good	Fair	Poor	N/A
Program schedule	☐	☐	☐	☐	☐
Accommodations	☐	☐	☐	☐	☐
Meals	☐	☐	☐	☐	☐
Contact with organizer	☐	☐	☐	☐	☐
Overall organization rating	☐	☐	☐	☐	☐

Overall evaluation	Excellent	Good	Fair	Poor	N/A
Overall rating of the course	☐	☐	☐	☐	☐

Would you recommend this course to a colleague? Yes ☐ No ☐

Comments

What was the best feature?

What changes would you make?

What will be the most helpful in your current/future job?

Other

Figure 6. *Evaluation form used to assess the course.*

- *Motivation for their own research by gaining an understanding of its relevance to industrial practice;*
- *Motivation to pursue teaching careers; and*
- *A major professional service opportunity.*

Finally, the course has also been useful as a vehicle to encourage undergraduate students from underrepresented minority groups to pursue graduate education and careers in biotech. In fact, for the last few years, our course has hosted a number of scholarship undergraduate minority students who have benefited from direct contact with industrial and academic scientists and engineers.

CONCLUSIONS

The course provides a unique and innovative way of combining graduate and continuing education in an area of critical importance to the biopharmaceutical industry. The integration of laboratories and lectures provides the participants with immediate feedback on the physical significance of theoretical relations and their relevance to industrial applications. It also provides opportunities to ask questions and to be challenged to provide answers to bioprocess problems in the informal setting of small teams. The highly multidisciplinary environment provides a great opportunity to understand the multifaceted nature of downstream processing. Finally, the teamwork setting of the laboratories and design exercise provides a unique opportunity for shared learning. We believe the general structure of our course can be successfully adapted to other areas within and outside the biotech field.

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