

Biopharma

Monitoring monoclonal antibody bioproduction processes with 2D-LC-UV

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Keywords

Process control, protein A, charge variants, size variants, cation exchange, size exclusion, SCX, SEC, heart-cut 2D-LC

Application benefits

- Heart-cut 2D-LC with protein A affinity chromatography (ProA) of cell culture samples enables titer determination and purification for subsequent charge or size variant analysis
- The method setup allows for highly efficient isolation of the monoclonal antibody (mAb) material. The Thermo Scientific™ ProPac™ 3R SCX Column, a high-performance strong cation exchange (SCX) column, facilitates the separation of mAb charge variants or serves as a trap column to focus the purified mAb fraction prior to transfer to size exclusion chromatography (SEC).
- The close monitoring of biosynthetic processes by the switchable 2D-LC at-line analysis enables timely intervention if required

Goal

At-line monitoring of multiple quality attributes, including mAb titer, charge variants, and aggregation of bioreactor samples.

Introduction

Biopharmaceuticals are a rapidly emerging class of therapeutics that differentiate in many ways from small-molecule pharmaceutical products. They come with a vast biological, immunological, structural, and physicochemical complexity that gives rise to various challenges in their analytical characterization and quality assurance.

Monoclonal antibodies comprise one of the largest categories of these biologics. During the different stages of the development and production of mAbs, a multitude of attributes needs to be characterized to ensure the safety and efficacy of the products.¹ The biosynthetic production processes—enzymatically or chemically induced post-translational modifications, aggregation or degradation of the proteins—give rise to numerous molecular variations, which need to be thoroughly monitored through the product lifecycle as product quality attributes (PQAs). Analytical techniques like liquid chromatography (LC) and mass spectrometry (MS) play a crucial role in this, but with the increasing complexity of the analytical tasks, the requirements to the analytical platforms grow. Thus, the utilization of two- and multi-dimensional LC (2D-LC, mD-LC) approaches has become more common in biopharma labs,^{1,2} with applications ranging from straightforward desalting of fractions for MS compatibility³ up to highly sophisticated multi-stage workflows including online reduction and enzymatic digestion for peptide mapping.⁴

Recently, a switchable multi-method 2D-LC-MS setup was showcased, tailored for the detailed monitoring of PQAs in the upstream processing of mAbs.⁵ In this study, supernatants were sampled from mAb producing bioreactors and analyzed for their mAb titer in the first dimension (1D) by protein A affinity chromatography (ProA). The 1D also served as a clean-up step from host cell material to enable two different options in the

second dimension (2D). The isolated mAb was transferred to a short SCX column, which was either eluted in a gradient to separate charge variants of the mAb or was switched in-line with a SEC column for the separation of size variants of the mAb. The direct coupling of the 2D with high-resolution accurate mass detection (HRAM) allowed for a deep characterization of the mAb and comprehensive insights into its glycan profiles, modifications, and aggregates at the intact level.

However, for the monitoring of well-established biosynthetic processes, HRAM MS may provide more information than required. Optical ultra-violet (UV) detection offers a streamlined workflow, enabling quick and efficient decisions during the production progression. This application note showcases the performance of an analogue heart-cut ProA-SCX(-SEC) 2D-LC setup with optical detection for straightforward process control. Again, method development was based on NISTmAb reference material (NIST™, RM 8671), while cell culture samples were drawn from two separate lab-scale bioreactors expressing a NISTmAb analogue (cNISTmAb) from Chinese hamster ovary (CHO) cells over the course of ten days (Figure 1). The integration of multiple LC techniques into a single 2D-LC setup allowed for the rapid assessment of several PQAs of the biosynthetic mAb material.

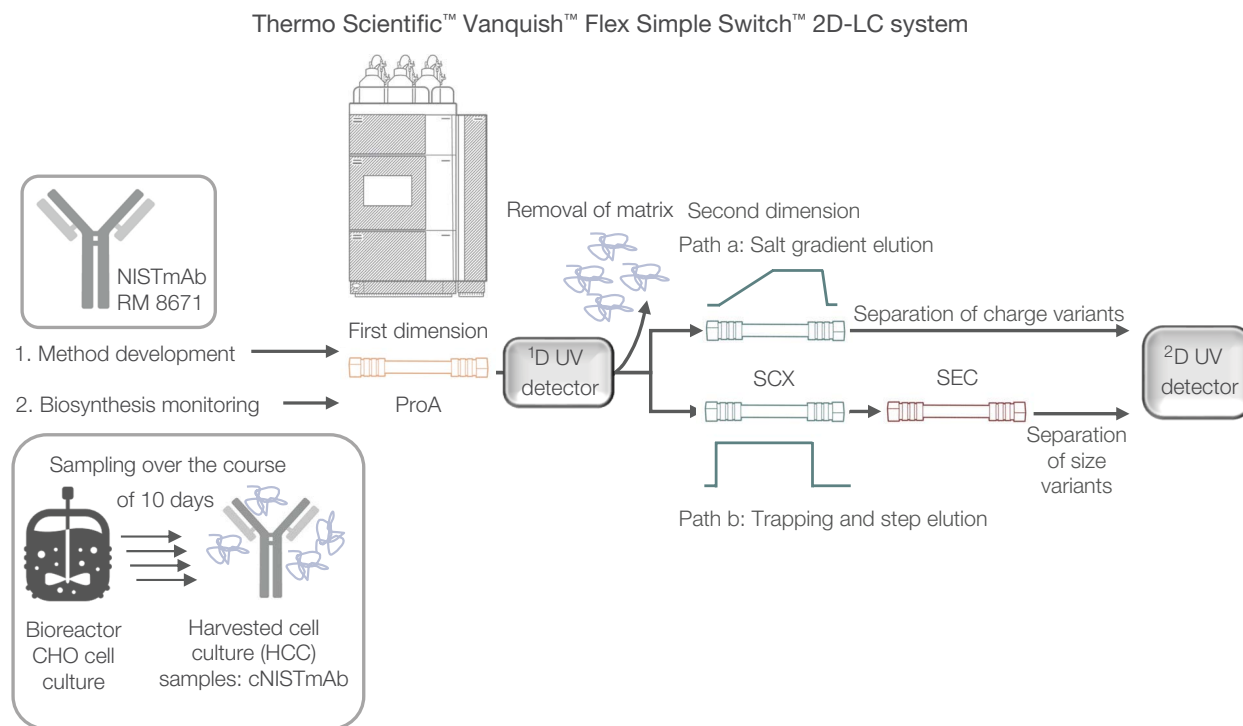


Figure 1. Overview of PQA monitoring of biosynthetic mAb production by heart-cut ProA-SCX-UV and ProA-SCX-SEC-UV. 1. NISTmAb standard was used for method development and optimization. 2. NISTmAb analog expressed in CHO cells (cNISTmAb) was sampled directly from the bioreactor over the course of 10 days for analysis.

Experimental

Chemicals

Chemical name	Part No.
Deionized water, 18.2 M Ω -cm resistivity or higher, from a Thermo Scientific™ Barnstead™ GenPure™ xCAD Plus Ultrapure Water Purification System	50136149
Thermo Scientific™ Chemicals Sodium phosphate, monobasic, anhydrous (NaH ₂ PO ₄)	389872500
Fisher Chemical™ di-Sodium hydrogen orthophosphate anhydrous (Na ₂ HPO ₄)	S/4520/53
Fisher Chemical™ Hydrochloric acid (HCl), 37%	H/1200/PB15
Fisher Chemical™ Sodium hydroxide (NaOH) solution (50%, w/w)	USSS254500
Fisher Scientific™ MES (2-(N-morpholino)ethanesulfonic acid) free acid monohydrate	BP300-100
Thermo Scientific™ Chemicals, Sodium chloride, 99.5%, for HPLC	446212500
NISTmAb RM 8671	8671 (NIST)

Sample handling

Item name	Part No.
Thermo Scientific™ Orion™ 3 Star pH Benchtop Meter	13-644-928
Thermo Scientific™ SureSTART™ 2 mL Short Thread Screw Glass Vials + Caps, Level 3, Amber	6PCK575W

Instrumentation

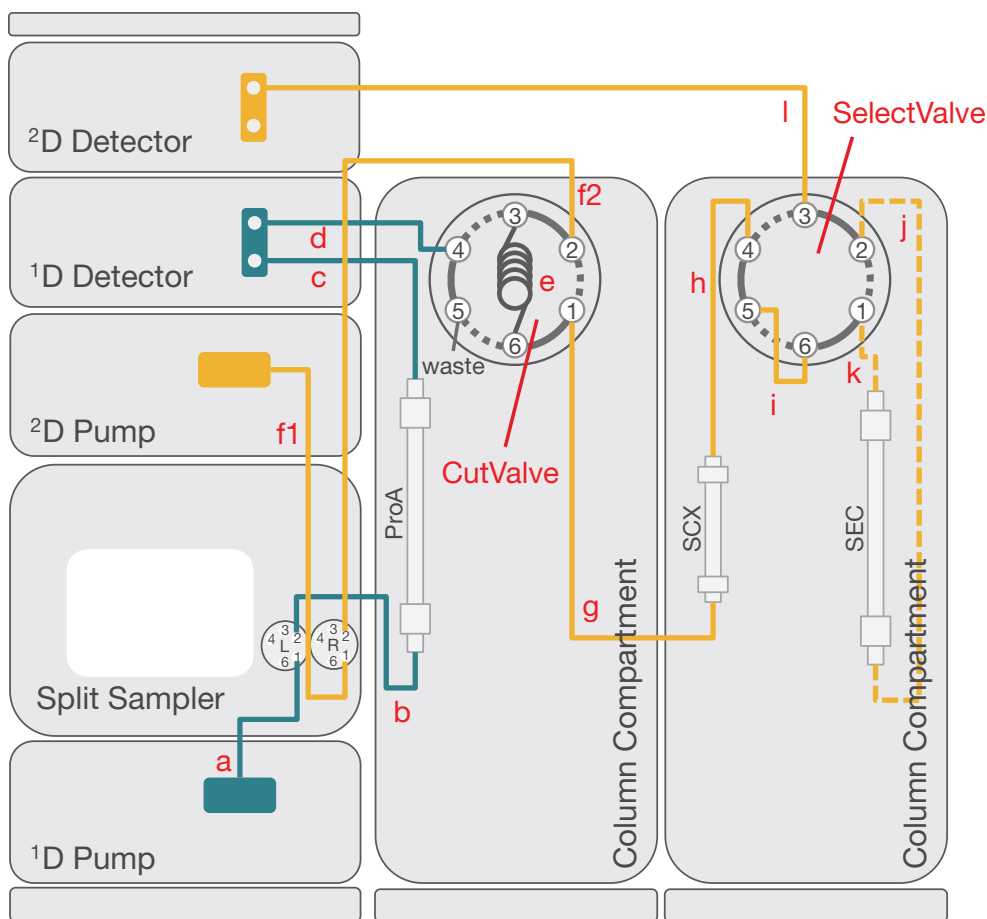
A Thermo Scientific™ Vanquish™ Flex Simple Switch™ 2D-LC System for loop heart-cutting was used, enabling the transfer of a fraction from a ¹D separation to a ²D separation. In the ²D, two separation mechanisms were selectable. The system consisted of the modules listed below.

The setup, including fluidic connections, is depicted in Figure 2.

Note: If desired, the fluidic connections can also be seamlessly updated to the new [Thermo Scientific™ Viper™ TQ UHPLC Fittings portfolio](#).

Module	Part No.
Thermo Scientific™ System Base Vanquish™ Horizon/Flex	VF-S01-A-02
Thermo Scientific™ Vanquish™ Binary Pump F (² D pump)	VF-P10-A-01
Thermo Scientific™ Vanquish™ Quaternary Pump F (¹ D pump)	VF-P20-A
Thermo Scientific™ Vanquish™ Dual Split Sampler FT*	VF-A40-A-02
Sample loop, biocompatible, MP35N, 1000 μ L (left injection unit, ¹ D)	6850.1980
Sample loop, biocompatible, MP35N, 100 μ L (right injection unit, ² D)	6850.1918
2x Thermo Scientific™ Vanquish™ Column Compartment H	VH-C10-A-03
2x Thermo Scientific™ Vanquish™ VH-C Valve 2-p 6-p 150 MPa bio	6036.2520
Sample loop, MP35N, 250 μ L	6823.0030
2x Thermo Scientific™ Vanquish™ Variable Wavelength Detector F (¹ D and ² D detector)	VF-D40-A
Thermo Scientific™ Vanquish™ Flow Cell, semi-micro bio, 7 mm, 2.5 μ L, for VF/VC-D40	6077.0300

*Optional: In case a direct injection to the ²D is not required and the system is solely used in 2D-LC mode, the installation of a [Thermo Scientific™ Vanquish™ Split Sampler FT](#) with a single injection unit might be preferred.



#	Connection	Part No.
a	Thermo Scientific™ Viper™ Capillary, ID × L 0.10 × 550 mm, MP35N	6042.2360
b	Thermo Scientific™ Vanquish™ Active Pre-heater, ID × L 0.10 × 380 mm, MP35N*	6732.0110
c	Viper Capillary, ID × L 0.10 × 450 mm, MP35N	6042.2350
d	Viper Capillary, ID × L 0.10 × 350 mm, MP35N*	6042.2340
e	Thermo Scientific™ Viper™ Fractionation Loop, 250 µL, MP35N	6823.0030
f	Viper Capillary, ID × L 0.10 × 450 mm, MP35N**	6042.2350
f1	Viper Capillary, ID × L 0.10 × 550 mm, MP35N	6042.2360
f2	Viper Capillary, ID × L 0.10 × 550 mm, MP35N	6042.2360
g	Vanquish Active Pre-heater, ID × L 0.10 × 380 mm, MP35N	6732.0110
h	Viper Capillary, ID × L 0.10 × 250 mm, MP35N	6042.2330
i	Viper Capillary, ID × L 0.10 × 65 mm, MP35N	6042.2306
j	Viper Capillary, ID × L 0.10 × 550 mm, MP35N	6042.2360
k	Viper Capillary, ID × L 0.10 × 150 mm, MP35N	6042.2320
l	Viper Capillary, ID × L 0.10 × 650 mm, MP35N	6042.2370
	1x Waste line, VH-D1	6083.2425

* Included in System Base Ship Kit VF-S01-A-02

** Replaces f1 and f2 if Split Sampler is installed instead of Dual Split Sampler

Figure 2. Fluidic scheme of the 2D-LC setup for ProA-SCX and ProA-SCX-SEC analysis. Teal and yellow lines represent the 1D and 2D flow paths, respectively. Solid yellow lines indicate the 2D flow path for ProA-SCX (corresponding to path a in Figure 1). The dotted yellow lines add to the 2D flow path for ProA-SCX-SEC (corresponding to path b in Figure 1). Fluidics can be updated to the new [Thermo Scientific™ Viper™ TQ UHPLC Fittings portfolio](#).

Samples

NISTmAb reference standard (NIST, RM 8671) was used for method development and titer calibration. The calibration curve was generated by the injection of 5, 10, 20, 100, and 200 µL of a NISTmAb solution of 0.05 µg/µL concentration, prepared in pure culture media.

The target mAb of the biosynthesis monitoring was a NISTmAb analog expressed by a new CHO cell line (NISTCHO, NIST

research grade test material 10197, now available as reference material 8675), referred to as cNISTmAb.⁶ Harvested cell culture (HCC) samples and corresponding reference culture media were provided by the National Institute for Bioprocessing Research and Training (NIBRT), Ireland. One 10 mL sample per day was collected from each of two lab-scale bioreactors operated in parallel over the course of 10 days, filtered using 0.45 µm and 0.2 µm PVDF filters, and stored at -20 °C until analysis.

Chromatographic conditions

Table 1. Chromatographic conditions. Left: ¹D ProA (purification for matrix removal); center: ²D SCX (separation of charge variants using a NaCl gradient); right: ²D SCX-SEC (SCX trapping, transfer to and separation of size variants by SEC).

	¹ D: ProA titer determination / purification		² D SCX: charge variants (path a in Figure 1)		² D SCX-SEC: size variants (path b in Figure 1)	
Column	Thermo Scientific™ MAbPac™ Protein A Antibody Analysis and Purification HPLC Column, 12 µm, 4 x 35 mm (Part No. 082539)		ProPac 3R SCX, 2 x 50 mm, 3 µm (Part No. 43103-052068) with Viper inline filter (Part No. 6036.1045)		Trap: ProPac 3R SCX, 2 x 50 mm, 3 µm (Part No. 43103-052068) Separation: Thermo Scientific™ MAbPac™ SEC-1, 5 µm, 4 x 300 mm (Part No. 074696)	
Mobile phase	A: 20 mM MES + 20 mM NaCl in water, pH 7.0* B: 20 mM MES + 20 mM NaCl in water, pH 2.5**		A1: 20 mM MES + 20 mM NaCl in water, pH 6.5** B1: 20 mM MES + 500 mM NaCl in water, pH 6.5**			
Flow rate	0.5 mL/min (0.1 mL/min from 10.0 min)				0.2 mL/min	
Injection volume	5-1,000 µL				¹ D fraction volume (175 µL)	
Gradient	Time [min]	%B	Time [min]	%B1	Time [min]	%B1
	0.0	0	0.0	0	0.0	0
	0.5	0	7.0	0	7.5	0
	0.5	100	22.0	30	7.5	58
	5.0	100	22.1	80	25.0	58
	5.0	0	25.0	80	25.0	0
	28.0/29.0	0	25.1	0	29.0	0
			28.0	0		
Column temperature	25 °C (still air)				30 °C (still air incl. active eluent preheating)	
Autosampler					5 °C	
UV detection					280 nm, 2 Hz, 2 s response time	
Valve position	CutValve: 0.0 min 6_1 6.14 min 1_2 6.50 min 6_1		SelectValve: 0.0 min 1_2		SelectValve: 0.0 min 1_2 7.5 min 6_1 25.0 min 1_2	

* pH adjusted by NaOH solution

** pH adjusted by HCl solution

To decrease the overall cycle time of the 2D-LC runs, overlapping injection preparation was applied by the *PrepareNextInjection* command in the Thermo Scientific™ Chromeleon™ CDS script editor entered at 3 min before run time end.

The configuration file, instrument methods, and ePanel are available for download in the [Thermo Scientific™ AppsLab™ Library of Analytical Applications](#).

Chromatography data system

Thermo Scientific™ Chromeleon™ 7.3.2 Chromatography Data System (CDS) was used for instrument control, data acquisition, and data processing.

Results and discussion

Monitoring of the biosynthetic processes is essential in the upstream processing of mAbs. The present application aimed for the development of a switchable 2D-LC-UV method setup suitable for the monitoring of multiple quality attributes of HCC samples drawn straight from a bioreactor, including mAb titer, charge variant, and size variant abundance.

2D-LC hardware and method setup

The Vanquish 2D-LC system, as outlined in Figure 2, was set up with one MAbPac Protein A column in the ¹D for sample clean-up and removal of host cell material, one ProPac 3R SCX column for the separation of charge variants, and one MAbPac SEC-1 column for the separation of size variants in the ²D. As an optional feature, the 2D-LC system configuration included a Vanquish Dual Sampler, which allowed an alternative system usage with independent dual 1D-LC fluidic paths. This setup not only facilitates straightforward method development in each dimension but also enables the analysis of mAb samples, which do not require an affinity clean-up step, directly for charge and size variants, without any replumbing.

All methods were developed and optimized with a NISTmAb reference standard and subsequently applied to the CHO cell culture samples expressing cNISTmAb (a NISTmAb analogue). The mobile phase systems were selected to be as consistent as possible over the three separation modes, all containing 20 mM MES and different concentrations of NaCl. The filtered HCC samples from the bioreactor were injected straight into the ¹D without any sample clean-up. Host cell material eluted without retention from the ProA column, while the mAb was captured due to the specific binding of the Fc region to protein A at neutral pH and was eluted afterwards by a step gradient at acidic conditions. After UV detection, the purified mAb fraction was transferred via the 250 μ L heart-cut loop to the ²D by switching the *CutValve*. The transferred fraction volume was limited to 175 μ L in the Chromeleon Fraction Collection parameters to reduce sample breakthrough.⁵ As illustrated in Figure 1, the mAb was subsequently captured by the short, high-efficiency ProPac 3R SCX column to continue with one of the two selectable ²D analysis. The elution of the mAb at low pH from the ProA column made the trapping at the SCX column highly effective. Both ²D options shared the same mobile phases, which enabled quick consecutive processing of either method without the need for re-equilibration to different conditions.

For charge variant analysis, the mAb was eluted from the SCX column with a linear NaCl gradient (path a in Figure 1), with the *SelectValve* kept in position 1_2 to have only the SCX column in-line with the ²D pump flow (solid yellow lines in Figure 2). For size variant analysis the *SelectValve* was switched to position 6_1 after the heart-cut to also bring the MAbPac SEC-1 column in-line (solid and dotted yellow lines in Figure 2). A step gradient to high NaCl concentrations (300 mM) then transferred the mAb in a narrow band from the SCX to the SEC column for subsequent isocratic separation (path b in Figure 1). The trap/elute procedure with the SCX column as an intermediate step before SEC introduction (ProA-SCX-SEC) solved a challenge that usually occurs when heart-cut fractions are directly transferred to the SEC column (ProA-SEC). SEC is highly susceptible towards band dispersion because the SEC mechanism is not capable of any re-focusing of compounds at the column head. As SEC cannot compensate itself for volume dispersion created by the heart-cut loop, the ProA-SCX-SEC approach significantly improved the peak shape and resolution of the SEC separation as shown in Figure 3.

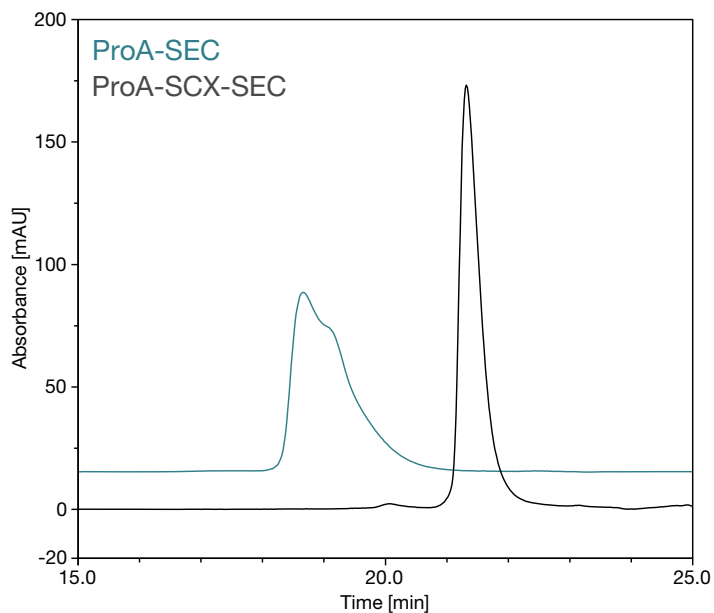


Figure 3. UV chromatograms obtained from ProA-SEC (teal) and ProA-SCX-SEC (black) setups with NISTmAb, demonstrating significant improvement of peak shape and width by the ProA-SCX-SEC procedure.

¹D affinity separation of HCC samples

A representative ¹D ProA-UV chromatogram of one HCC sample drawn on the third day from the bioreactor is shown in Figure 4, with indication of the heart-cut fraction for the transfer to the ²D. Highly reproducible retention times (RTs) of the mAb with a relative standard deviation (RSD) of only 0.15% over 40 sample injections ensured a reliable and reproducible time-triggered heart-cutting procedure.

For titer determination, a linear calibration curve (Figure 5, left) was prepared by injecting 0.25–10 µg NISTmAb RM

onto the ProA column. Excellent linearity with a coefficient of determination $R^2 = 0.99965$ was obtained. Injected sample volumes were gradually decreased over the 10 days of the biosynthetic process from 1,000 µL to 250 µL, to obtain UV signals of cNISTmAb within the calibrated range. The cNISTmAb titer increased from 15 µg/mL on day 1 up to 82 µg/mL on day 10, as summarized in Figure 5 (right).

After the purification of the mAb peak by heart-cutting, the downstream processing can be selected to either analyze charge variants (path a in Figure 1), or size variants (path b in Figure 1).

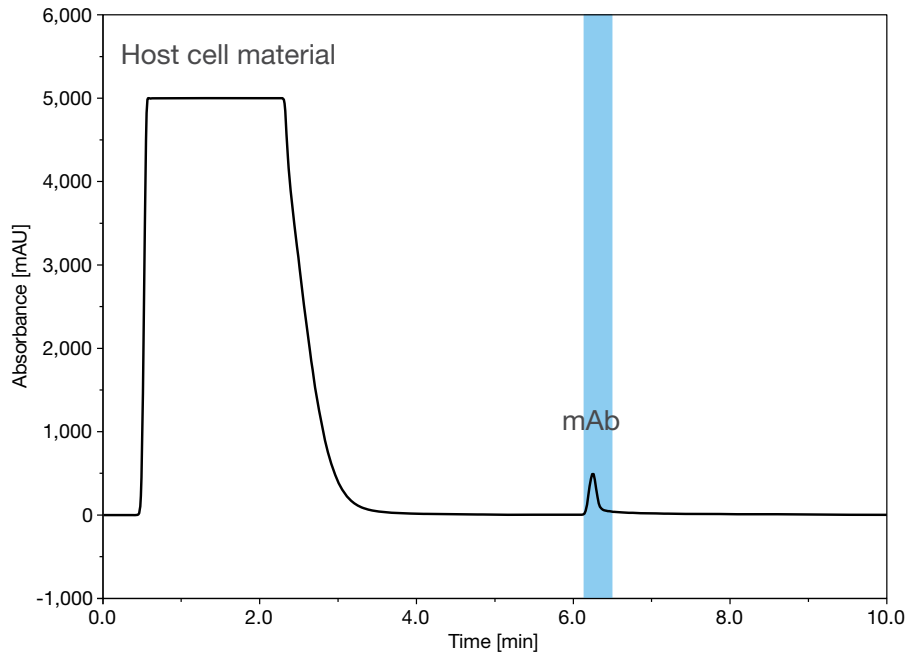


Figure 4. ¹D ProA-UV chromatogram obtained from the HCC sample drawn on day 3 with the heart-cut fraction indicated by the blue shading.

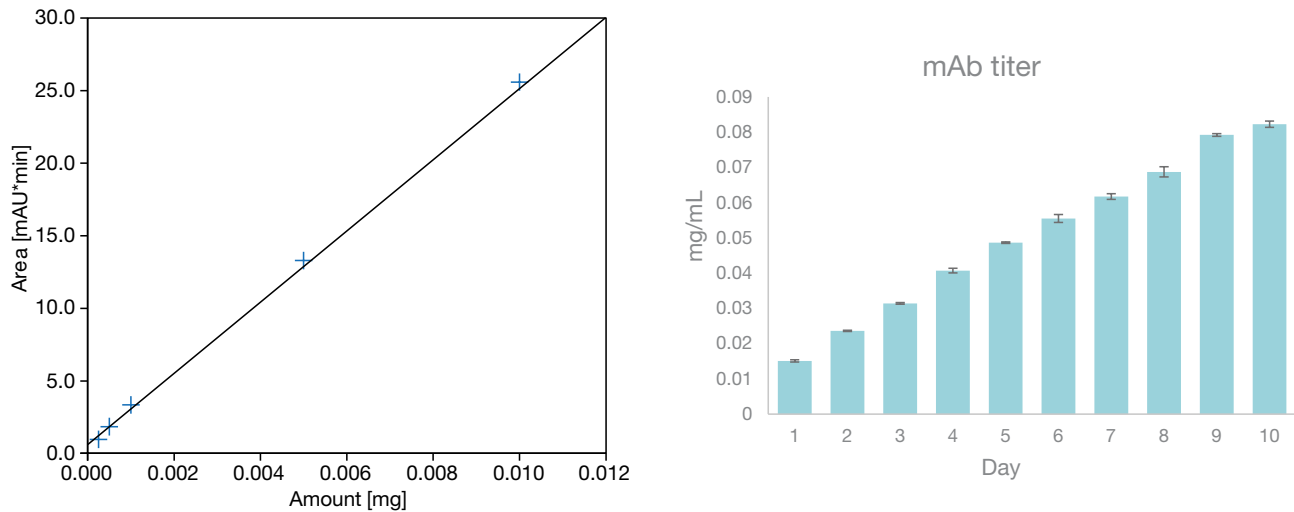


Figure 5. mAb titer calibration curve (left) and titer determination of HCC samples from ¹D ProA-UV (right). Samples were drawn from the bioreactors over the course of 10 days. Bars represent the titer averaged over two injections of the two samples drawn per day from each of the parallel cultures, with error bars indicating the RSD.

²D charge variant analysis of HCC samples via ProA-SCX

For the separation of charge variants in the ²D, the purified and captured mAb was eluted by a linear salt gradient from the SCX column (Figure 1, path a). Peaks from up to 6 acidic and 13 basic variants could be separated from the cNISTmAb main peak (M), depending on the progress of the biosynthesis (e.g., acidic variant A-1 was only detected from day 8 on). Two chromatograms from samples drawn on day 3 from the two bioreactor batches are shown in Figure 6.

Attributes for process monitoring in charge variant analysis with optical detection typically focus on the occurrence of peaks and their absolute or relative abundance. As the sample injection volume was altered over the 10-day period in our study, relative area or height ratios were considered. Figure 7 summarizes the area of the main peak (relative to all integrated areas) over the 10 days of sampling from both reactors. For the two batches, very consistent trends were seen, starting at $\approx 46\%$ relative area on day 1, increasing to $\approx 55\%$ on day 7, and plateauing till the end of the study.

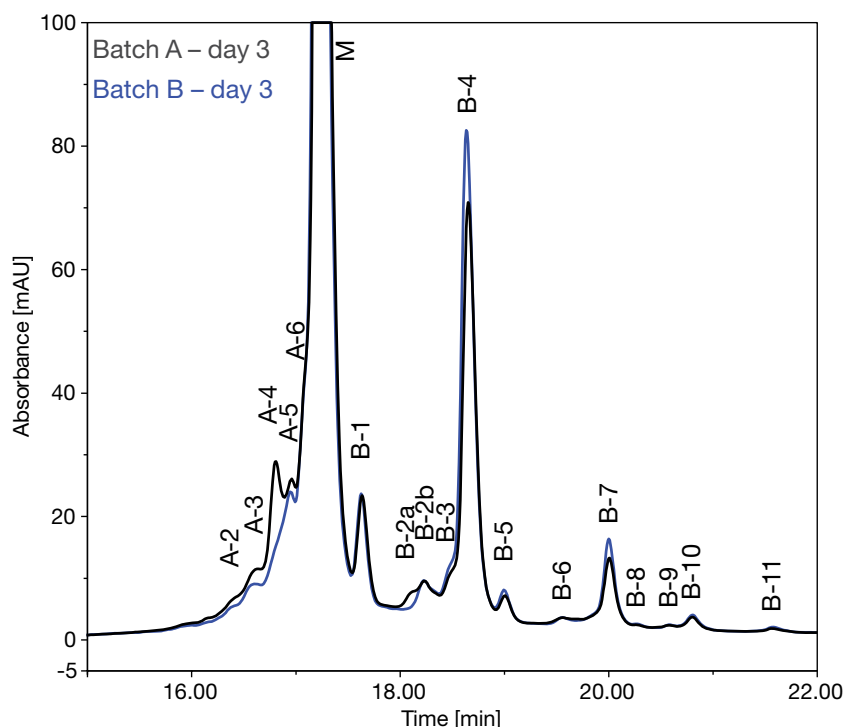


Figure 6. Comparison of ²D SCX-UV chromatograms of cNISTmAb from HCC samples drawn from both bioreactors on day 3.

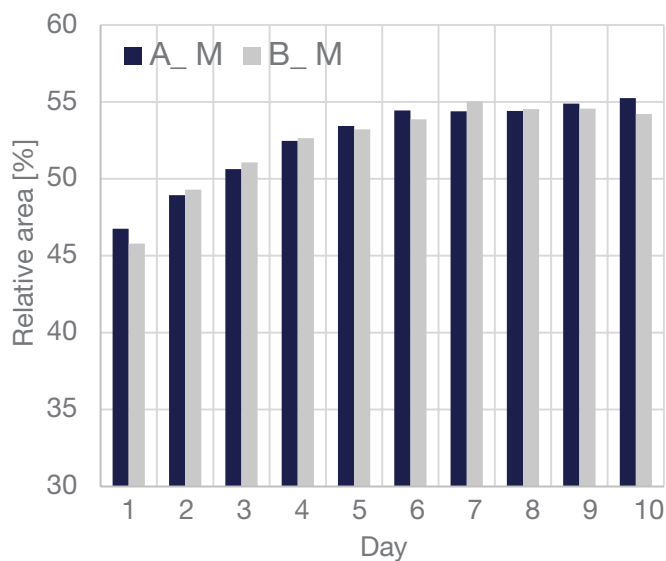


Figure 7. Development of ²D SCX main peak M relative area over 10 days in both bioreactor batches (batch A, batch B).

Congruent trends of both batches were also observed for most acidic and basic charge variant peaks. One example is shown in Figure 8A for basic peak B-1, which occurred with a fairly constant height of 10%–12% relative to the main peak over the course of the biosynthesis. However, some divergences between the two batches were observed. The relative peak height of acidic peak A-4 (Figure 8B) was equivalent on days 1 and 2 for both batches, falling from approximately 15% down to around 6%. Deviating results were observed over the next two days, but from day 5 onwards, the batches coincided again. Similarly, the trends for basic peak B-4 diverged significantly only on days 3 and 4 between the two batches (Figure 8C). The differences on day 3 are also apparent from the chromatogram overlay in Figure 6. In a real-world scenario for process monitoring, such deviations might be representative for inadvertent deviations from specified PCAs during the biosynthesis of a mAb product. The quick and straightforward at-line monitoring of HCC samples by ProA-SCX can provide valuable information, enabling critical corrective process interventions in real time.

²D size variant analysis of HCC samples via ProA-SCX-SEC

For the size variant analysis of the mAb isolated from the ¹D, the MAbPac SEC column was coupled with the ProA-SCX setup in the ²D (Figure 1, path b). In Figure 9, chromatograms of samples from one bioreactor drawn at an early and late stage of the process are compared. Due to the intermediate re-focusing of the mAb by the SCX column, well-resolved peaks could be detected for the mAb monomer, a low molecular weight (LMW) fraction and two high molecular weight (HMW) fractions by SEC. The abundance trends of these aggregates (HMW) and fragments (LMW) are summarized in Figure 10 and show consistent behavior for both batches. The LMW fraction decreased from approximately 10% relative area on day 1 within a few days down to a constant level of around 4%. Meanwhile, the HMW-1 fraction increased from ≈2% to ≈3.5% in the first few days but decreased again from day 5 onwards when the HMW-2 peak started to be detected, possibly indicating a shift in the nature of the aggregates. In process control, the monitoring of HMW and LMW species is critical with respect to product safety and efficacy.

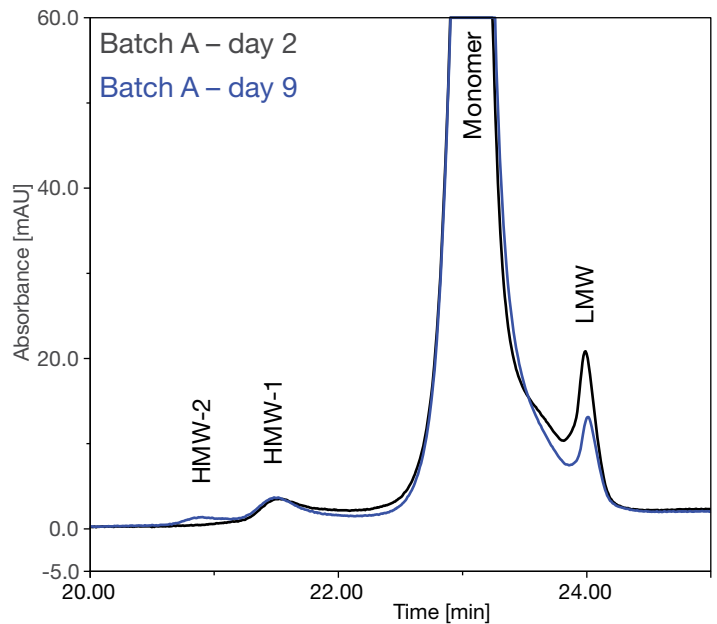


Figure 9. ²D chromatogram of ProA-SCX-SEC analysis of HCC samples drawn on days 2 and 9.

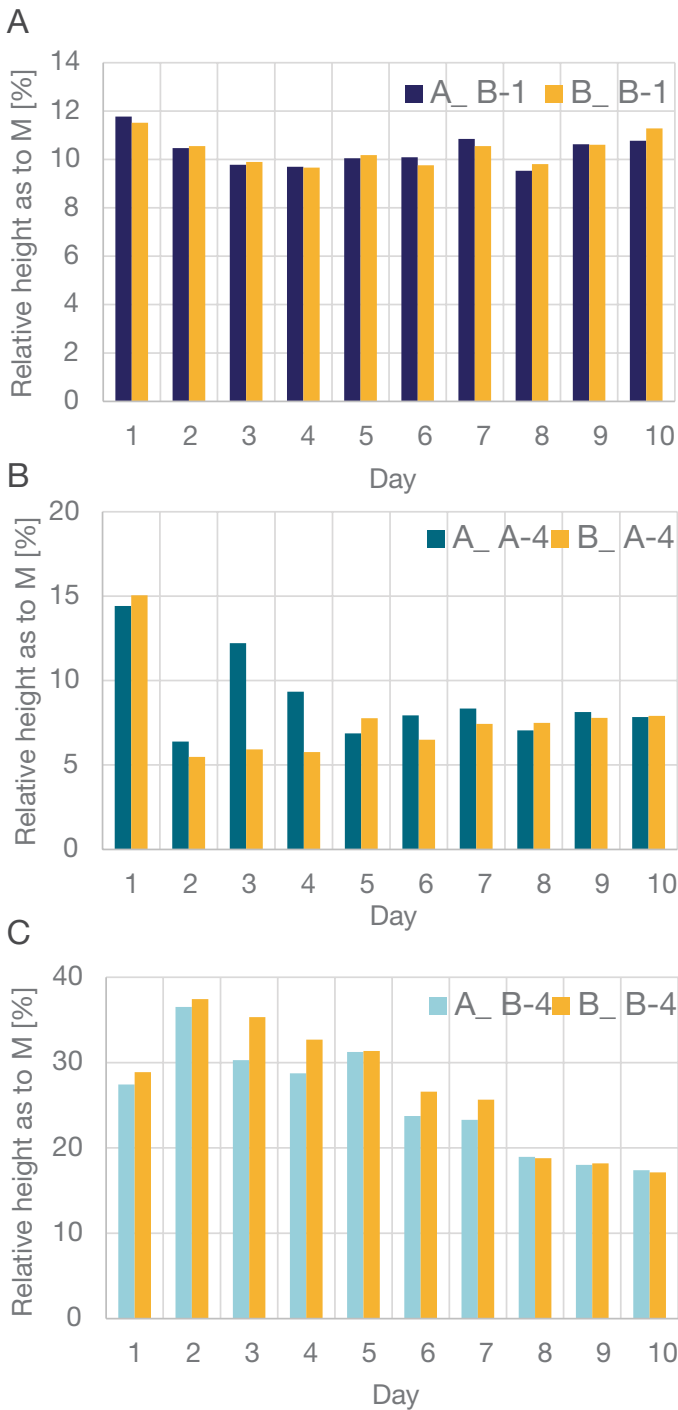


Figure 8. Peak heights of three charge variant peaks relative to the main peak M detected in the ²D SCX of HCC samples over 10 days (batches A and B). A: basic variant peak B-1, B: acidic variant peak A-4, C: basic peak B-4. Peak assignment according to Figure 6.

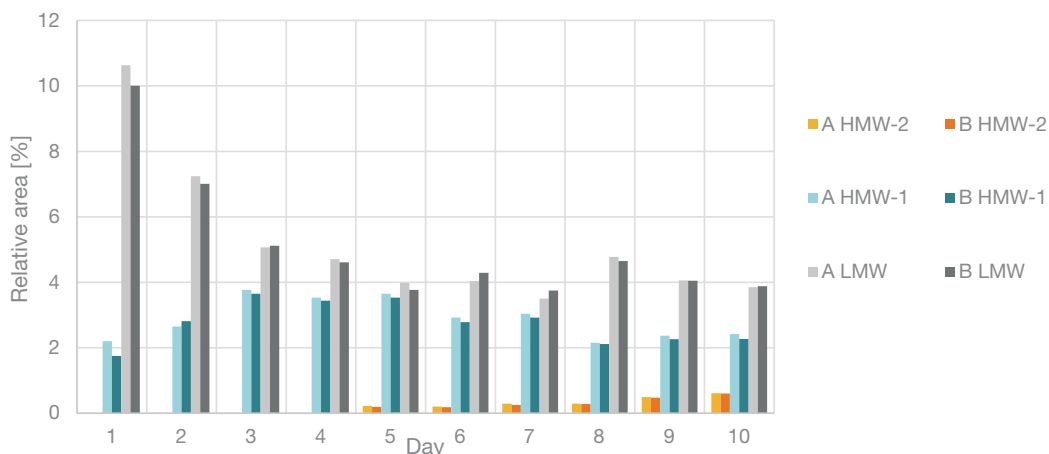


Figure 10. Relative area of LMW, HMW-1, and HMW-2 fractions monitored from batches A and B over the 10-day cell culture production period analyzed by ProA-SCX-SEC.

In summary, the presented 2D-LC system setup comprising a switchable 2-column setup using ProA-SCX and a 3-column setup using ProA-SCX-SEC with UV detection allows for rapid and straightforward biosynthesis monitoring of cNISTmAb, enabling for quick decisions in real-time.

Conclusion

- The switchable heart-cut 2D-LC approach facilitated straightforward upstream monitoring of multiple PQAs over a 10-day production cycle of cNISTmAb directly from cell culture samples
- Titer determination upon ProA affinity purification revealed mAb concentrations between 15 and 82 µg/mL
- Charge variant analysis of the purified mAb allowed for the abundance monitoring of up to 6 acidic and 13 basic charge variant peaks, revealing deviations between the two bioreactor batches
- Size variant analysis using an SCX-SEC column setup enabled the assessment of LMW and HMW fractions over the course of the 10-day period
- Close and in-time monitoring of biosynthetic processes provides valuable insights for process control and optimization, enabling timely interventions to ensure product quality and safety

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