Refractive Index as a PAT tool in biopharma protein filtration

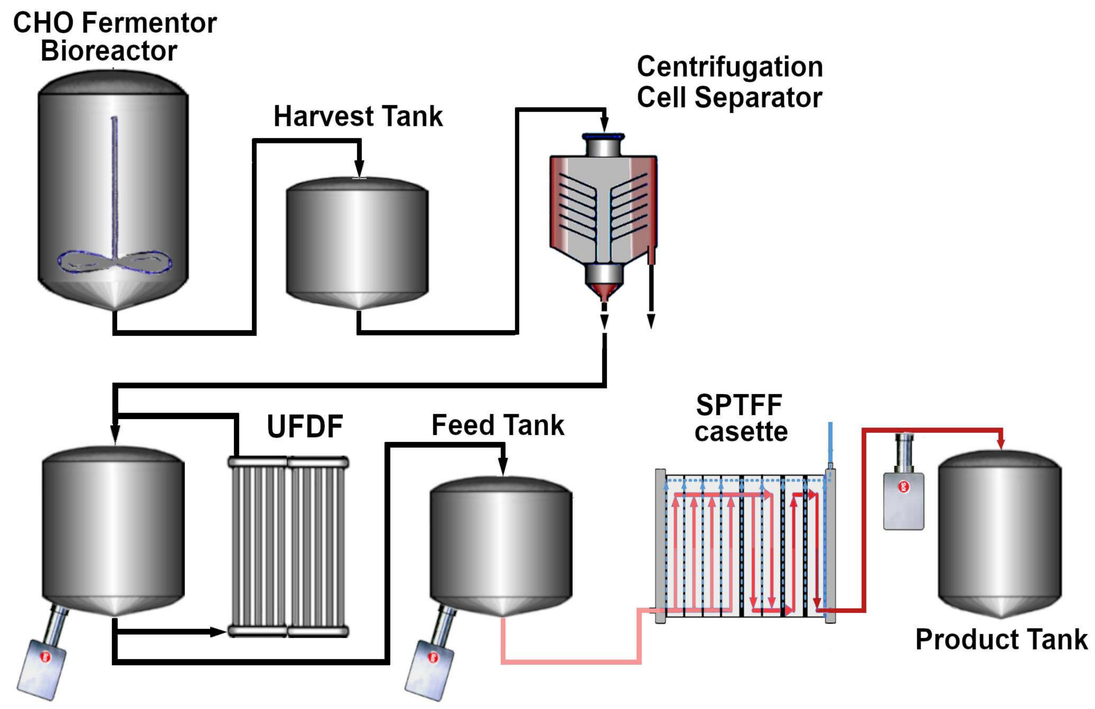
For further information:
Anupama Bhandari
anupama.bhandari@kxstechnologies.com

Marcus Kavaljer
marcus.kavaljer@kxstechnologies.com
KxS Technologies Oy
www.kxstechnologies.com

Meinhard Missbach
office@missbach.co.at
Meinhard Missbach GmbH

Real-time release testing (RTRT) is redefining quality assurance in pharmaceutical manufacturing. By integrating inline PAT tools, automation, and data analytics, RTRT enables continuous monitoring and control of critical process parameters, replacing end of-of-batch offline testing with real-time, data-driven batch release. The result is reduced manufacturing cycle time, data-driven batch control, and full regulatory traceability throughout production.

KxS Process refractometer DCM-20 with Ingold connection is a proven Process Analytical Technology (PAT) sensor for monitoring protein concentrations directly in Tangential flow filtration (TFF) systems and their collection tanks. The continuous data generated by KxS inline refractometer directly supports Quality by Design (QbD) and Real Time Release Testing (RTRT) frameworks, providing validated, real-time process data needed for timely release of the production batches.



1 Introduction to real-time filtration process control

TFF is increasingly being employed in downstream processes to purify, concentrate, and formulate drug substances e.g., mAb's. TFF consists of ultrafiltration and diafiltration (UFDF) steps.

Ultrafiltration concentrates and purifies proteins and diafiltration performs buffer exchange. UFDF steps are designed to achieve predefined target protein concentrations and buffer conditions required for the drug substance.

Protein concentration is a critical quality attribute – a property that must be precisely controlled. Traditionally, mass balance or volumetric ratio calculations are used to estimate target retentate volumes and process endpoint for UFDF operations.

Samples are taken manually at discrete points or at the end of the operation and analyzed in laboratory to verify the protein concentrations. Results arrive with a delay, while the process continues to run without real-time feedback.

And by the time the offline results are available, the process endpoint may already have been missed, resulting in overconcentrated product that requires reprocessing. Batch release awaits offline laboratory results, resulting in downtime between downstream processing steps. At commercial scale, an out-of-specification batch means costly reprocessing and downtime results in financial loss.

What if you could see exactly what happens in your process — in real time — at every moment of the run.

The KxS DCM is a proven PAT sensor that mounts directly into UFDF process streams and collection tanks, enabling continuous, inline protein concentration monitoring and control with no need for manual sampling, without delays or gaps in the process data.

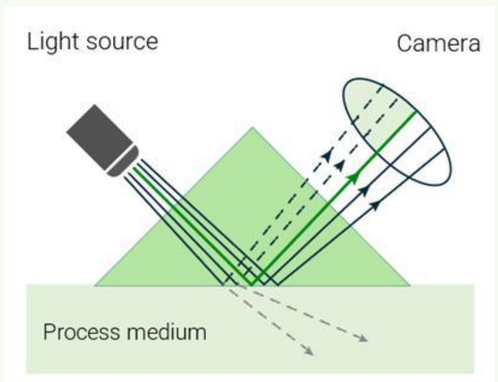
KxS DCM features unique 1" Ingold and 1.5" Tri-clamp connections exclusively available from KxS Technologies (protected by Utility Model FI 13493 Y1).

2 Measurement principle

KxS DCM-20 employs the physical phenomenon of refractive index to define liquid concentration. Refractive index (RI) measurement is based on Snell's law and the critical angle of total reflection to provide precise readings.

Light from an LED is directed at the optical window-liquid interface; as concentration changes, the resulting light-shadow pattern is captured by a digital camera and converted into RI.

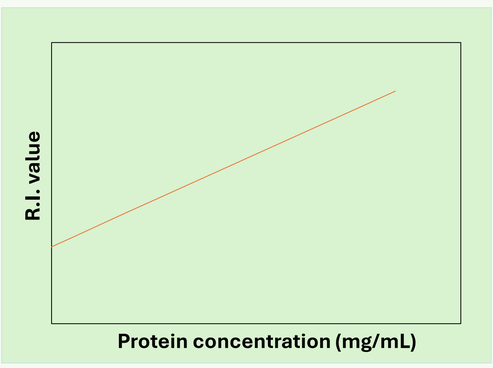
Image illustrating measurement principle of a process refractometer.



Sensor calibration: A linear relationship between protein concentration, temperature and refractive index is established. The relationship is defined by measuring the refractive index values of the solution over a range of protein concentrations and temperatures for a given TFF operation. The linear relationship is determined for each protein/buffer solution.

No recalibration is required after factory sensor calibration. A measurement accuracy of ±0.5 mg/mL can be achieved in full range 0-300 mg/ml.

Chemical curve for protein mg/mL per R.I. at reference temperature of 20 °C.



3 Results

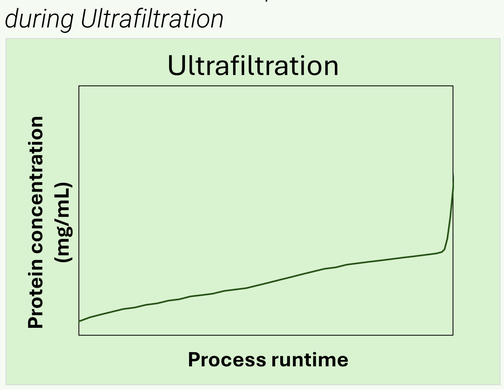
Ultrafiltration concentrates proteins as smaller solutes such as salt, water and molecules pass through the membrane filters.

Diafiltration involves continuously adding fresh buffer while the existing buffer is removed, keeping the retentate volume and protein concentration constant.

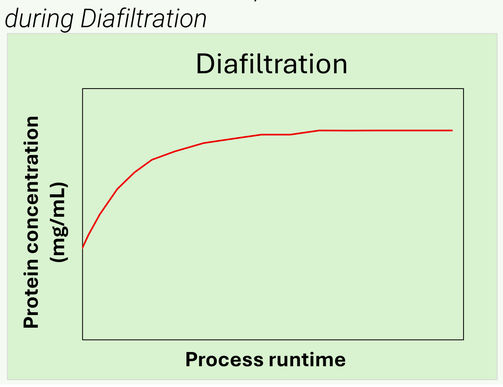
KxS DCM-20 is installed directly in the TFF system and collection tank. Process data is captured continuously and visualized as live concentration trend, accessible directly via the user interface.

During UF, DCM-20 tracks the rising concentration profile in real-time. During DF, DCM-20 confirms that protein concentration remains stable and within specifications across the entire buffer exchange.

Protein concentration profile of one batch during Ultrafiltration



Protein concentration profile of one batch during Diafiltration



4 Benefits

The KxS DCM-20 successfully monitors protein concentrations continuously in UFDF operations, generating a complete process profile for each batch. Inline RI measurement accurately tracks rising protein concentration during ultrafiltration, enabling precise endpoint detection, and confirmed concentration stability within specification during diafiltration.

This level of data density goes far beyond what discrete offline sampling can provide, giving process engineers the insight needed to understand the process behavior, establish expected concentration trends, and define meaningful deviation tolerances.

When integrated as part of the control strategy, the continuous concentration data enables CPPs to be actively maintained within specification – shifting from offline end-of-batch verification to proactive in-process control, a cornerstone of the QbD framework.

The batch process profiles generated by the DCM-20 provides a robust foundation for process development and scale-up, enabling process profile comparison across batches and to identify variability, validate control strategies, and build process understanding that transfers confidently from development to high-scale continuous manufacturing.

The continuous data record generated by the inline refractometer supports PAT and RTRT frameworks — providing the validated, real-time process evidence needed to release batches instantly, without the delays associated with offline laboratory testing. This results in faster batch release, reduced downtime, and improved process consistency, reducing manufacturing cycle times and minimizing costly downtime between downstream processing steps.

KxS DCM-20 with 1" Ingold process connection installed in a collection tank