Transforming inline viscometer into a PAT tool for measuring real-time protein concentration in TFF operation

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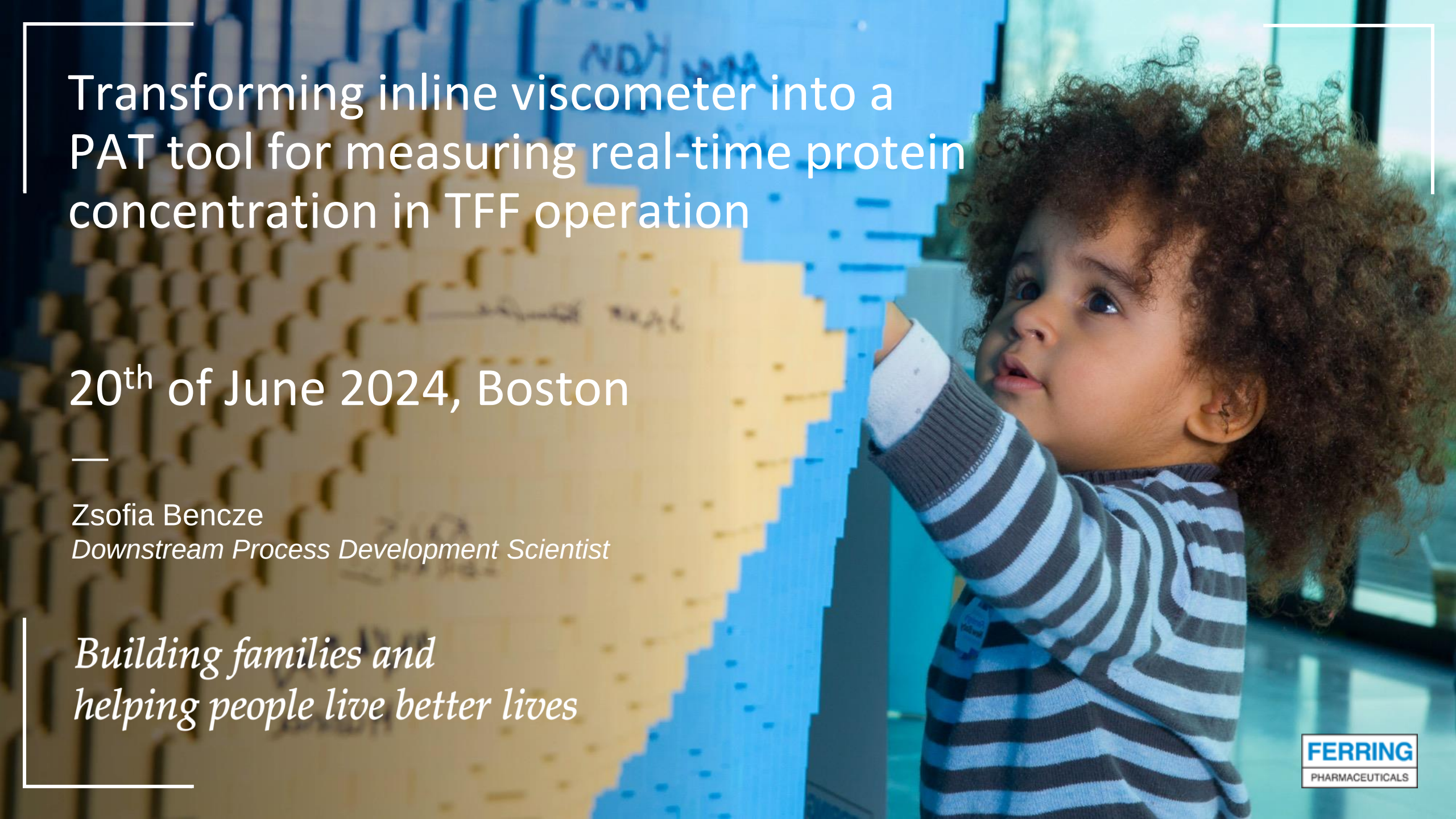
Building families and helping people live better lives



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Company overview

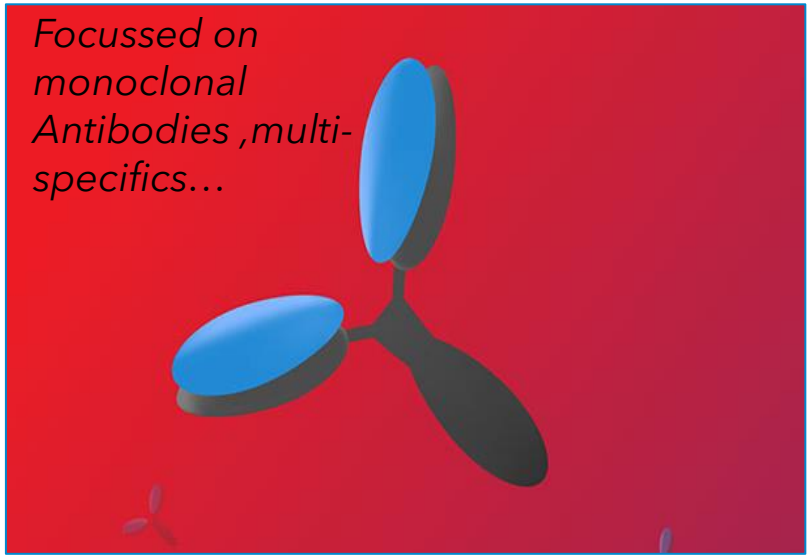
- Privately owned, research-driven, specialty biopharmaceutical group committed to building families and helping people live better lives
- Leader in reproductive medicine and maternal health, and in specialty areas within gastroenterology and urology
- At the forefront of innovation in microbiome-based therapeutics and uro-oncology intravesical gene therapy
- Ferring has a full spectrum of products from conception to birth
- Founded in Malmö, Sweden in 1950, headquartered in Switzerland
- Global company with over 7,000 employees in more than 50 countries, and distribution in over 100 countries
- 2023 revenue: EUR 2.2 billion*
  2023 R&D investment: 16%

*USD 2.3 billion – CHF 2.1 billion

Ferring Biologics Innovation Centre (FBIC)

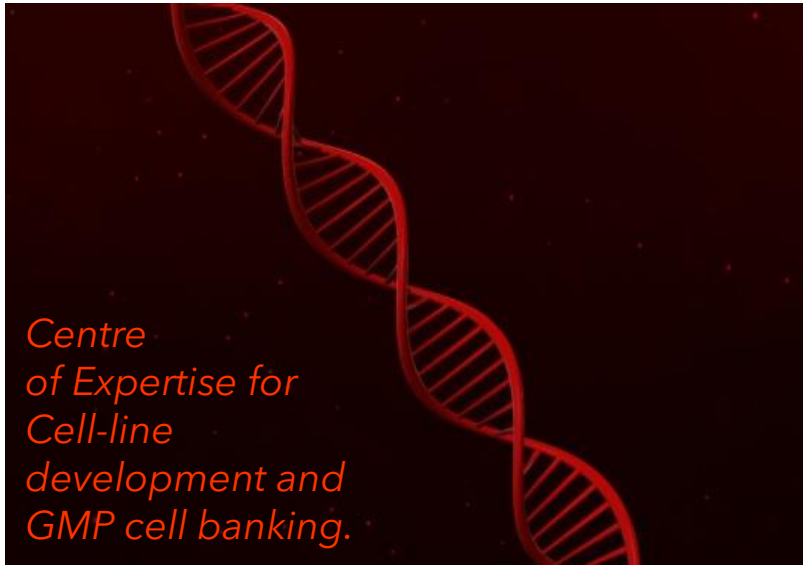
A unique asset within Ferring network.

Focussed on monoclonal Antibodies ,multi-specifics…

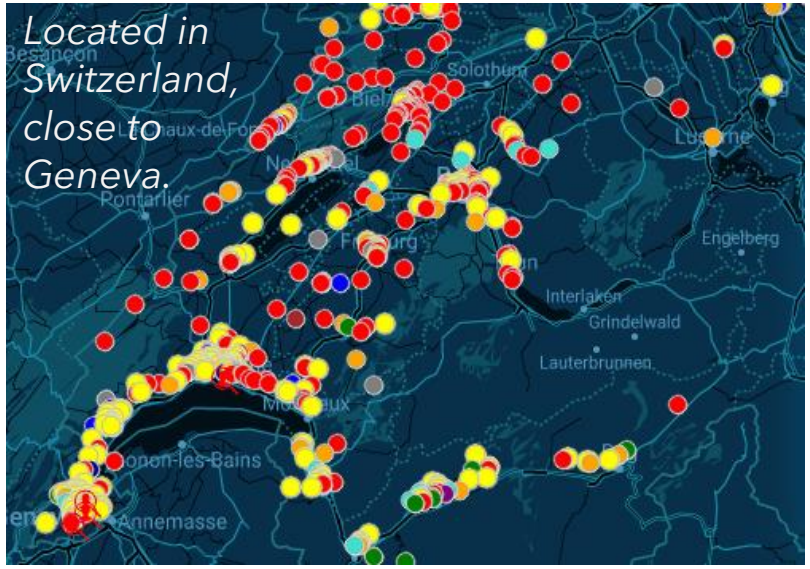


…and viral vectors processes.

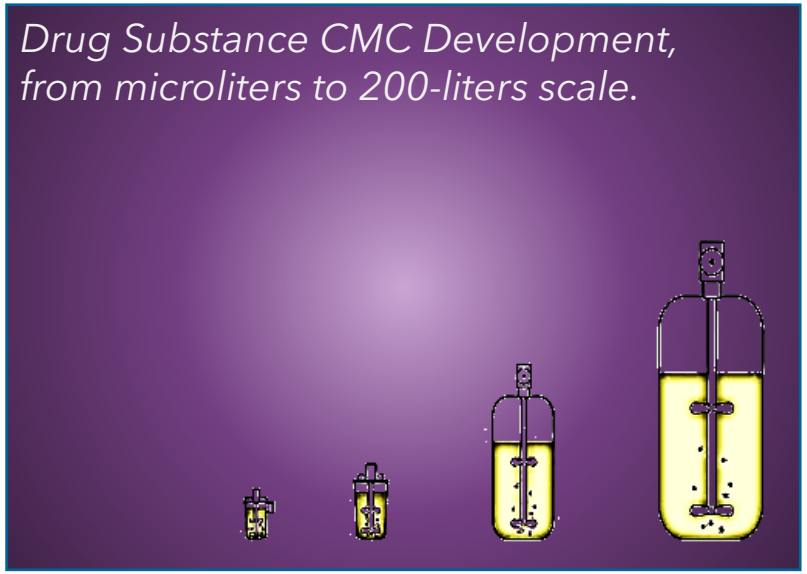
Centre of Expertise for Cell-line development and GMP cell banking.



Located in Switzerland, close to Geneva.



Drug Substance CMC Development, from microliters to 200-liters scale.



Why implementing Process Analytical Technologies (PATs) in a TFF setup is the go-to approach?

Give back time to the scientists!

Understand our process

Predict (impact of buffer systems, fluid temperature, concentration, …etc.)

Speed-up process design and optimisation

Reduce experimental cost

Secure scale-up

First real-time protein concentration monitoring at FBIC with *Levitronix* inline viscometer

Tangential Flow Filtration (TFF)

A unit operation, that is often performed manually in the industry even at manufacturing scale.

mAb – IgG1

A straightforward, robust molecule to work with.

Expected outcome

Calibration and integration of inline viscometer for real-time protein concentration estimation, shorter processing time, lower cost of goods and less resources.

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Stages of implementation

Outline the Project

- Automated monitoring and control.
- Integrated feedback loops based on PAT
- Increased robustness and accuracy, supplementing balance readout with viscosity.
- Scalable, transferable, single use, and affordable solution, made from certified material.

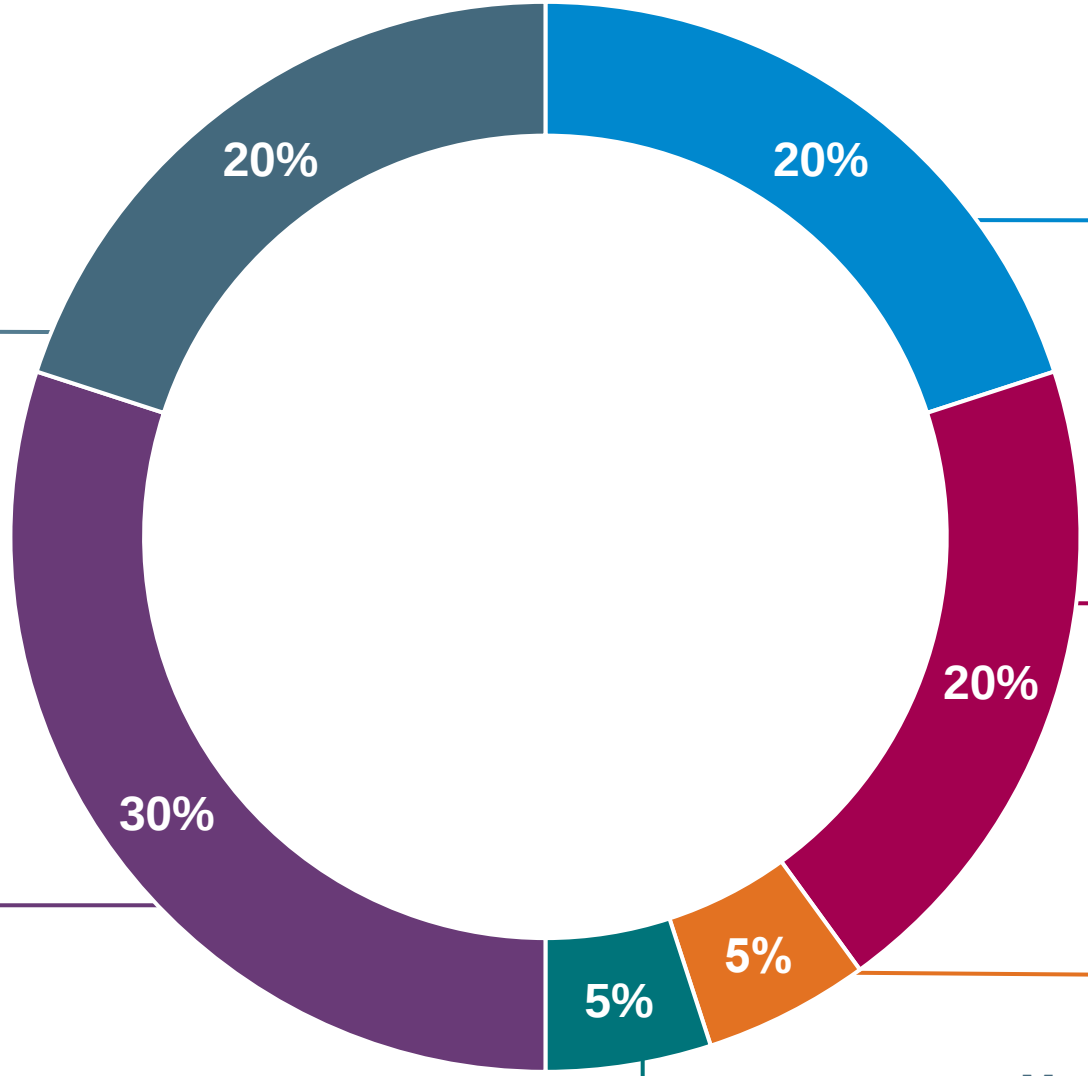
Laboratory

- Process design for an IgG1 molecule.
- Two different formulation recipes.
- Calibration of the inline viscometer for each buffer system .
- High concentration UF/DF/UF runs with each buffer systems.
- Upgraded TFF system with Levitronix PATs (inline viscometer) and consols.
- Automated TMP control for less manual interaction.

Model Building

- Prediction model building based on calibration experiments.
- Viscosity data can be transformed to concentration data.
- Reference concentration and viscosity measurement to confirm inline and at-line data. (Solo VPE for A280, microVISC for viscosity).

Time investment overview by stages



Outline of Project

Material generation

Laboratory Analytics

Model Building

Calibration

Application

Description of experiments

Inline Viscosimeter Calibration Experiments

- 10 datapoints
- Start concentration: 140 mg/mL.
  End concentration 5 mg/mL.
- Temperature ramping from 20-28 ˚C for each datapoint
- Calibration of viscometer PAT tool with two commercial formulation recipes for IgG1.

High Concentration Tangential Flow Filtration

- Two different formulation buffer recipe tested
- 5 g of IgG1 material was loaded on 0.02 m^2 membrane.
- UF1: 5 to 50 mg/mL.
- Diafiltration: 7 DVs, controlled by flowmeter, balances, conductivity and inline viscometer PAT.
- UF2: up to 140 mg/mL.

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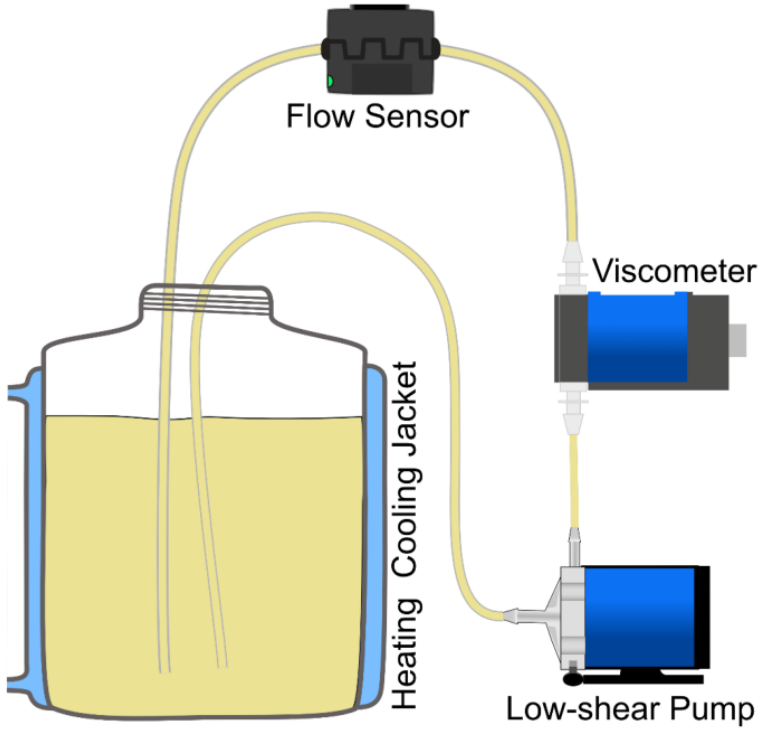
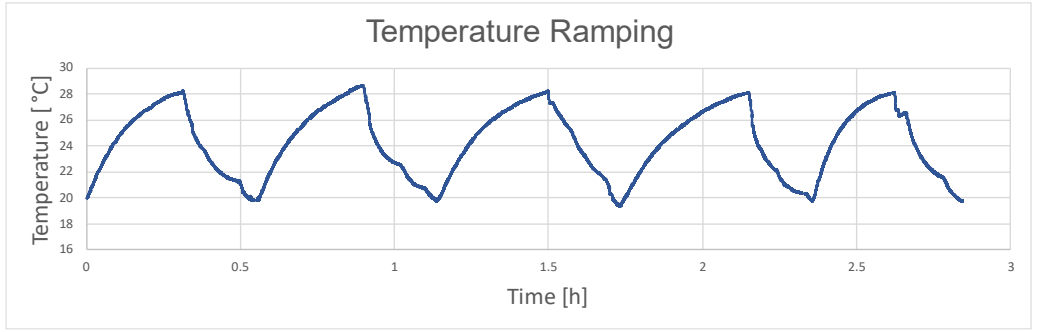
Calibration setup for prediction model building



Calibration procedure

a) Starting material: The mAb solution in formulation buffer at 140 mg/mL.
b) Temperature was ramped from 20-28 °C, while measuring the resulting viscosity.
c) IgG1 sample was diluted to the next, selected lower concentration value, and steps (a) – (c) were repeated until the lowest concentration value of 5 mg/mL.



Samples for analytics were taken at 27.5 °C.

Online viscosity	Viscometer PAT	Levitronix	continuous data recording
Offline viscosity	microVISC	Rheosense	reference
Offline validated concentration	Solo VPE	C-Technologies, Repligen	reference
Offline concentration for monitoring	Nanophotometer	Implen	confirming volume changes and monitoring concentration change
SEC-HPLC	Vanquish Flex	Thermo Scientific	quality information

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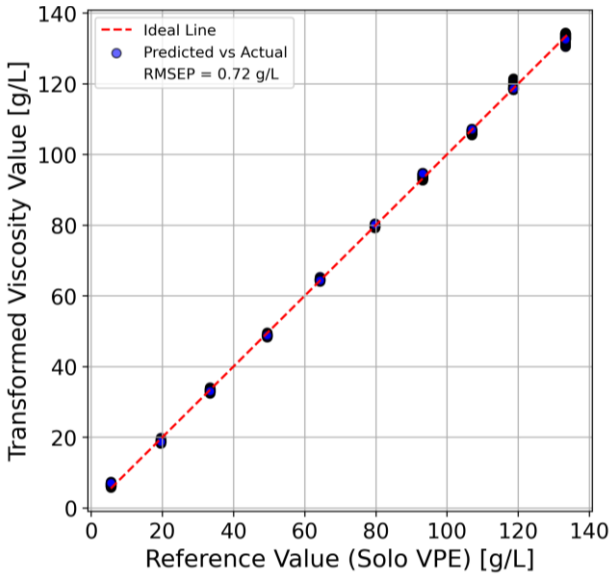
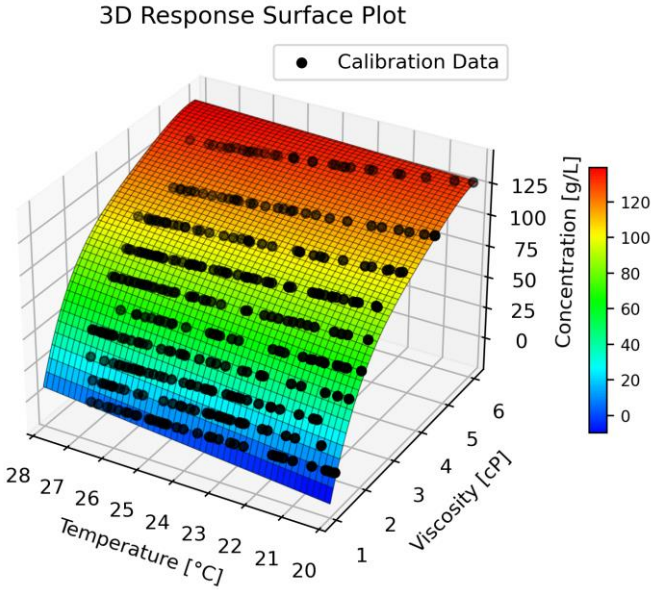
Calibration results of data analyses

$$C = -228 + 218\eta + 3T - 0.4\eta T - 68\eta^2 + 11\eta^3 - 0.6\eta^4$$

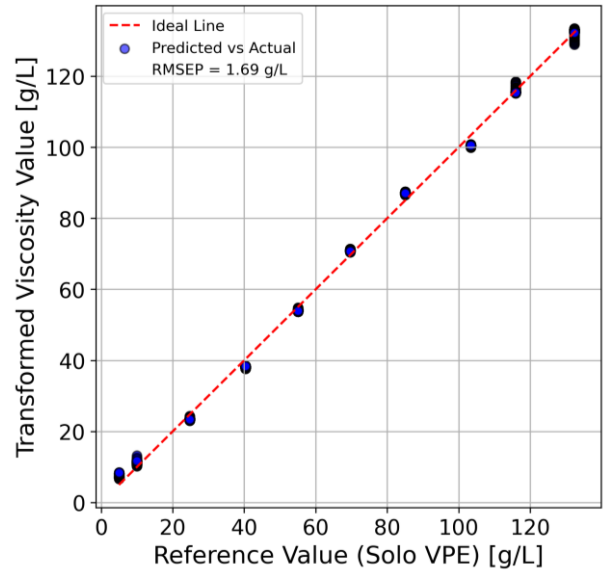
$C = Concentration\ [g/L]$
$\eta = Viscosity\ (cP)$
$T = Temperature\ (°C)$

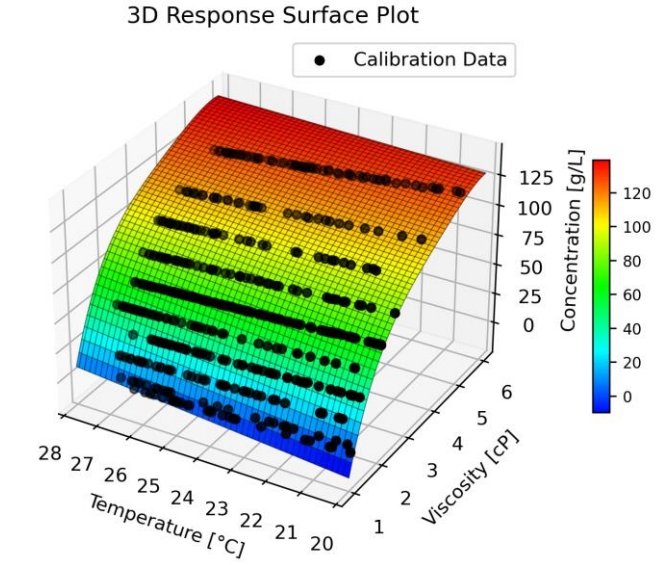




$$C = -196 + 204\eta + 2.6T - 0.25\eta T - 69\eta^2 + 12\eta^3 - 0.8\eta^4$$

$C = Concentration\ [g/L]$
$\eta = Viscosity\ [cP]$
$T = Temperature\ [°C]$





- The IgG1 solution in buffer 2 shows lower viscosity at the same concentration and temperature.
- Information on viscosity of IgG1 solutions at different concentration could aid process design and optimal buffer system selection.

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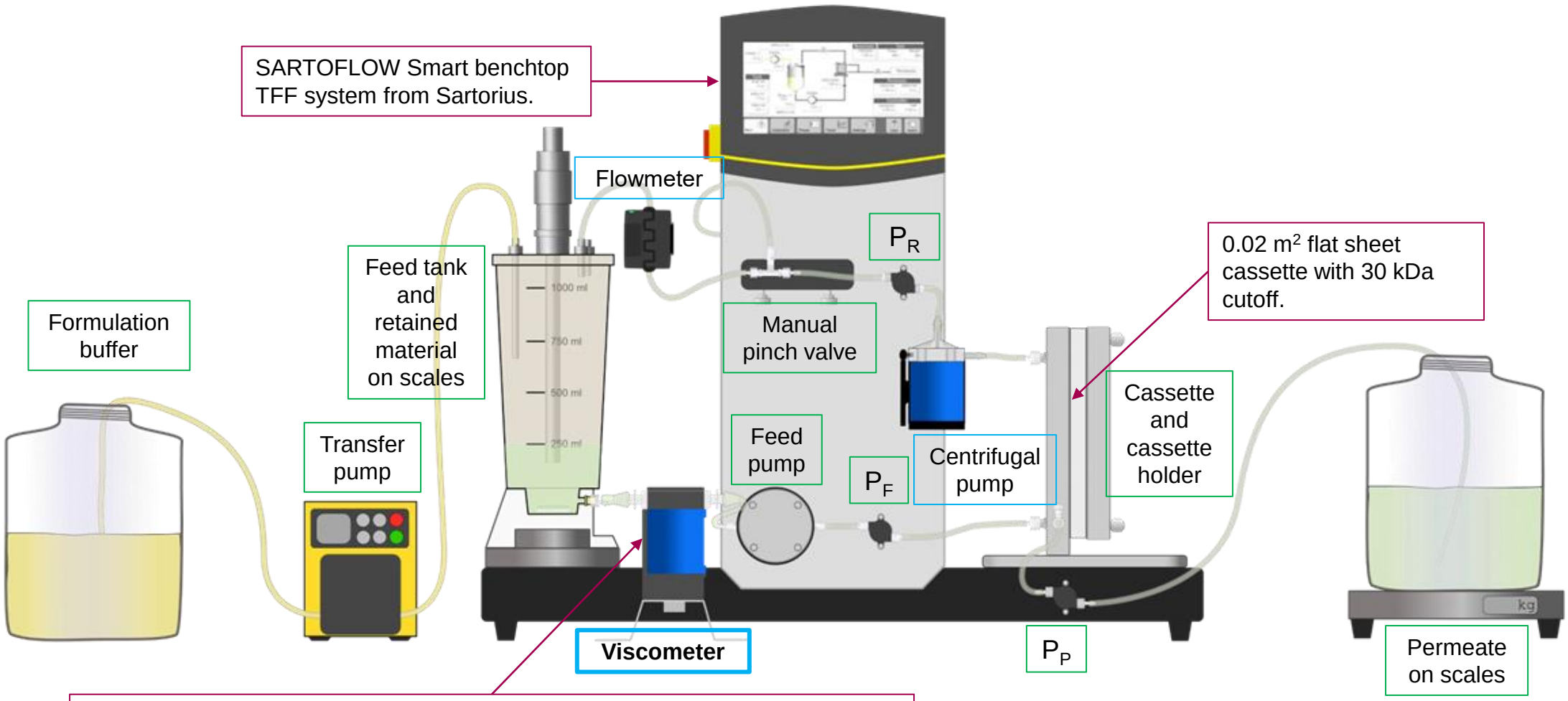
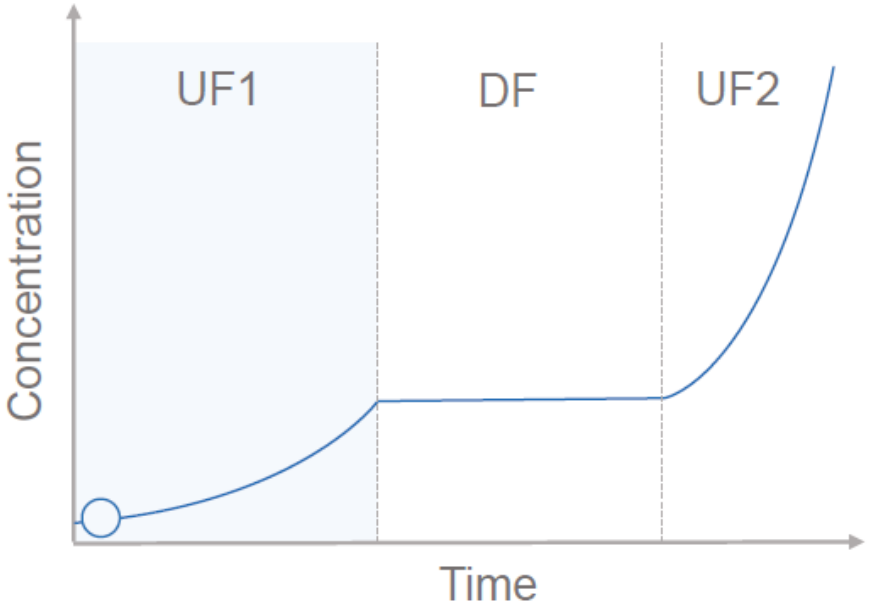
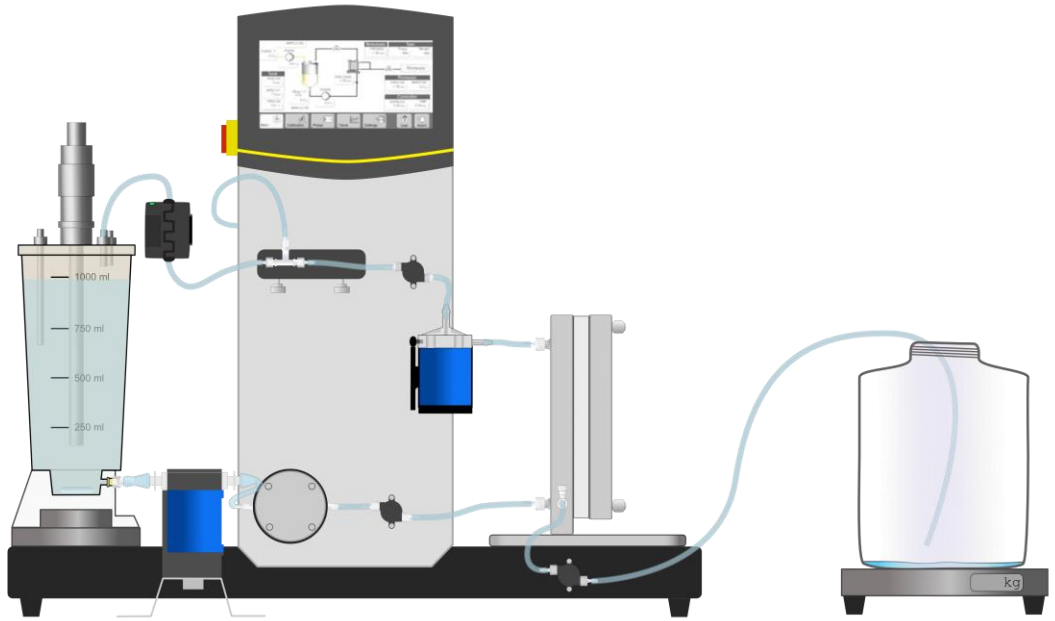
System setup



Process Highlights

Start 1st Ultrafiltration





Start Concentration (mg/mL)	5
Start Volume (mL)	1000
Transmembrane Pressure (bar)	1.2

Online viscosity	Viscometer PAT	Levitronix	continuous data recording
Offline viscosity	microVISC	Rheosense	reference
Offline validated concentration	Solo VPE	C-Technologies, Repligen	reference
Offline concentration for monitoring	Nanophotometer	Implen	confirming volume changes and introducing phase change
SEC-HPLC	Vanquish Flex	Thermo Scientific	quality information

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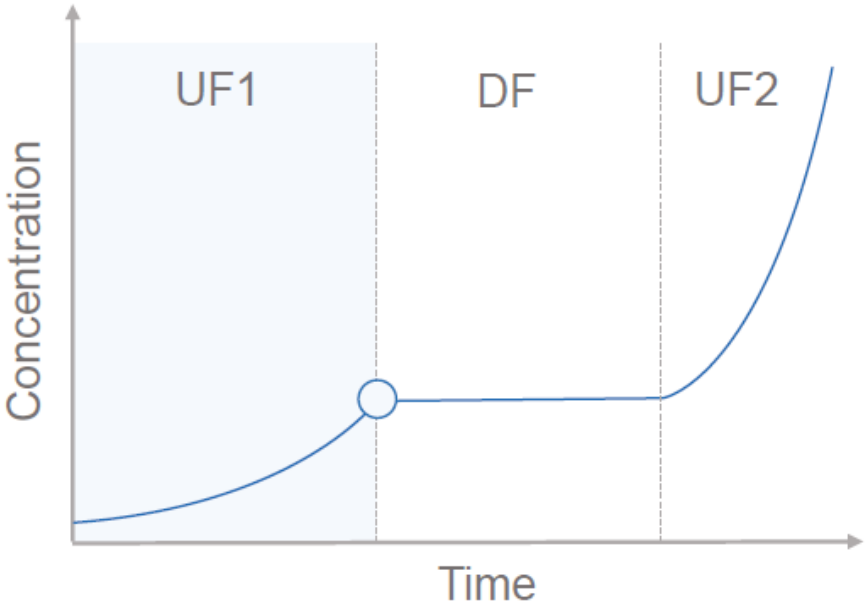
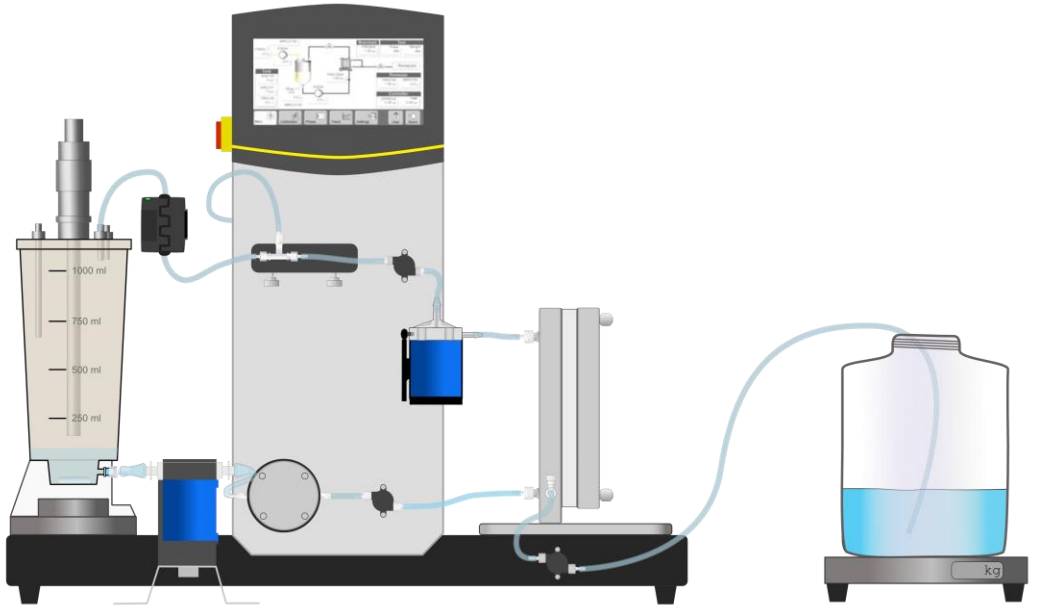
Process Highlights

Finish 1st Ultrafiltration and start Diafiltration





End Concentration (mg/mL)	50
End Volume (mL)	100
Duration (min)	105
Transmembrane Pressure (bar)	1.2

Online viscosity	Viscometer PAT	Levitronix	continuous data recording
Offline viscosity	microVISC	Rheosense	reference
Offline validated concentration	Solo VPE	C-Technologies, Repligen	reference
Offline concentration for monitoring	Nanophotometer	Implen	confirming volume changes and introducing phase change
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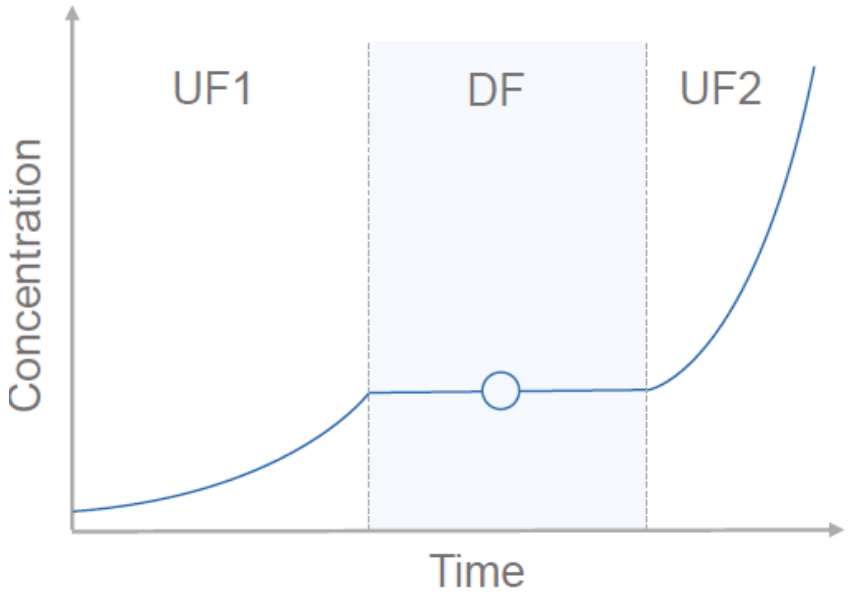
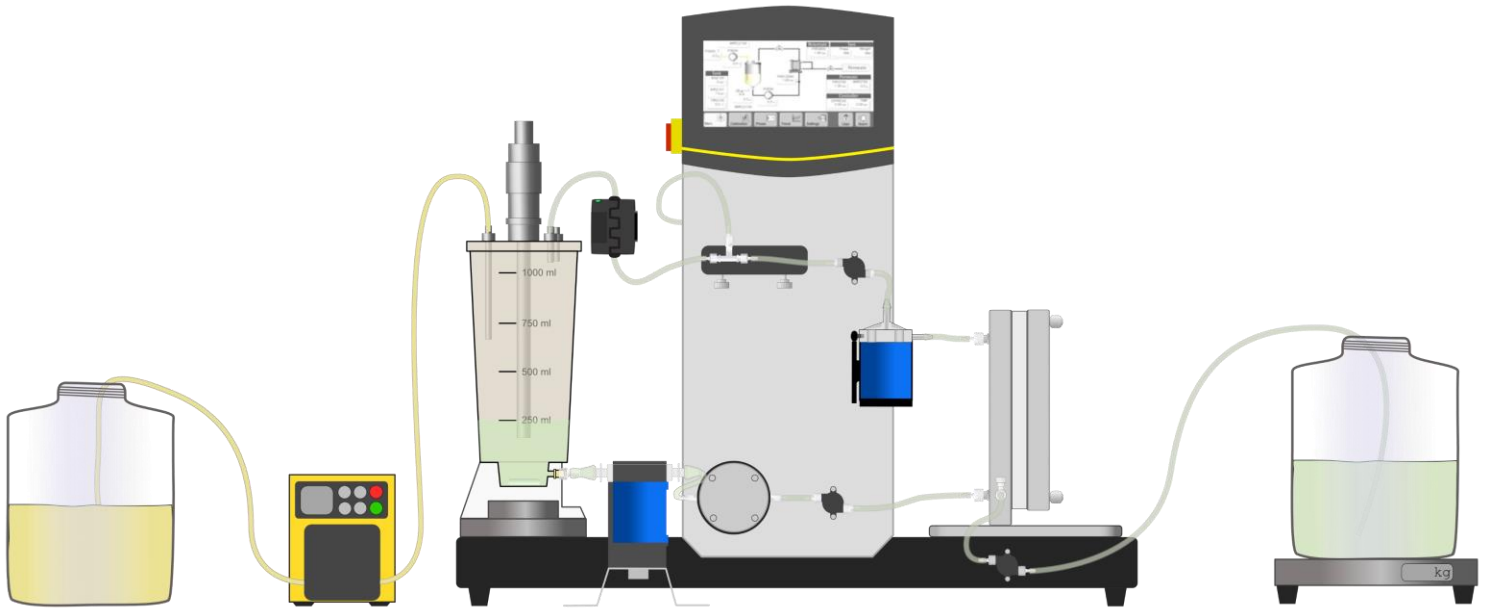
Process Highlights

During Diafiltration





Start Concentration (mg/mL)	50
Start Volume (mL)	100
End Concentration (mg/mL)	50
End Volume (mL)	100
Diafiltration Volumes	7
Duration (min)	80
Transmembrane Pressure (bar)	1.2

Online viscosity	Viscometer PAT	Levitronix	continuous data recording
Offline viscosity	microVISC	Rheosense	reference
Offline validated concentration	Solo VPE	C-Technologies, Repligen	reference
Offline concentration for monitoring	Nanophotometer	Implen	confirming volume changes and introducing phase change
SEC-HPLC	Vanquish Flex	Thermo Scientific	quality information

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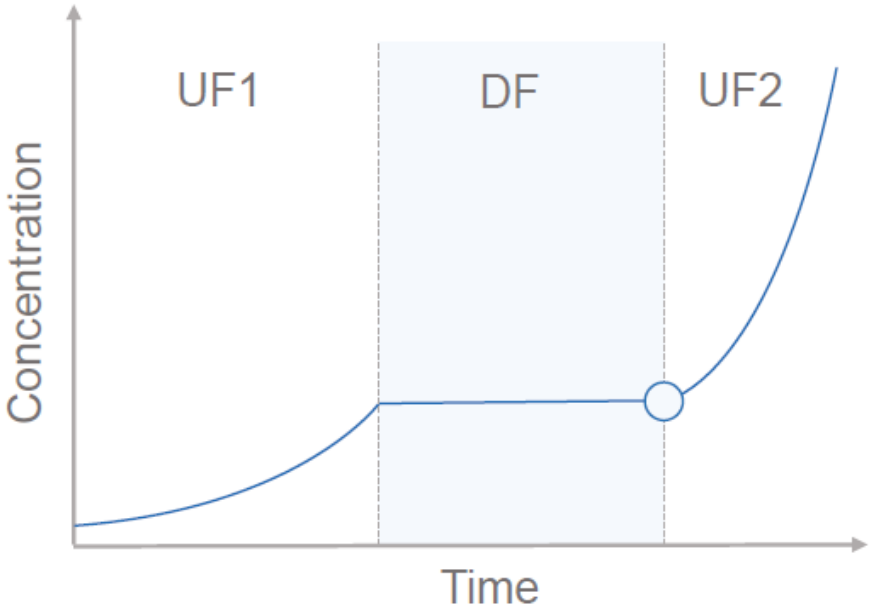
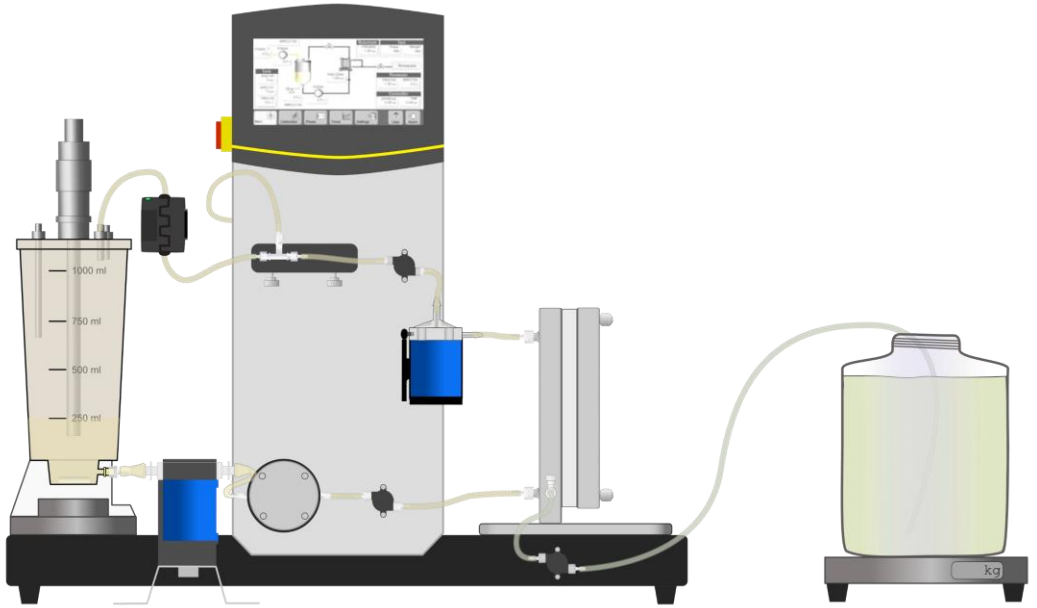
Process Highlights

Finish Diafiltration and start 2nd Ultrafiltration





Start Concentration (mg/mL)	50
Start Volume (mL)	100
Transmembrane Pressure (bar)	1.2

Online viscosity	Viscometer PAT	Levitronix	continuous data recording
Offline viscosity	microVISC	Rheosense	reference
Offline validated concentration	Solo VPE	C-Technologies, Repligen	reference
Offline concentration for monitoring	Nanophotometer	Implen	confirming volume changes and introducing phase change
SEC-HPLC	Vanquish Flex	Thermo Scientific	quality information

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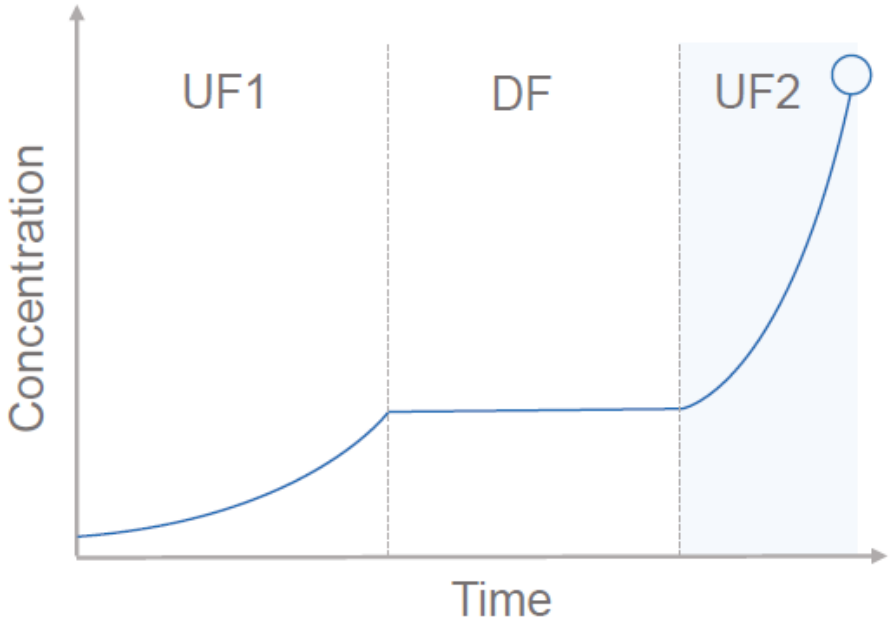
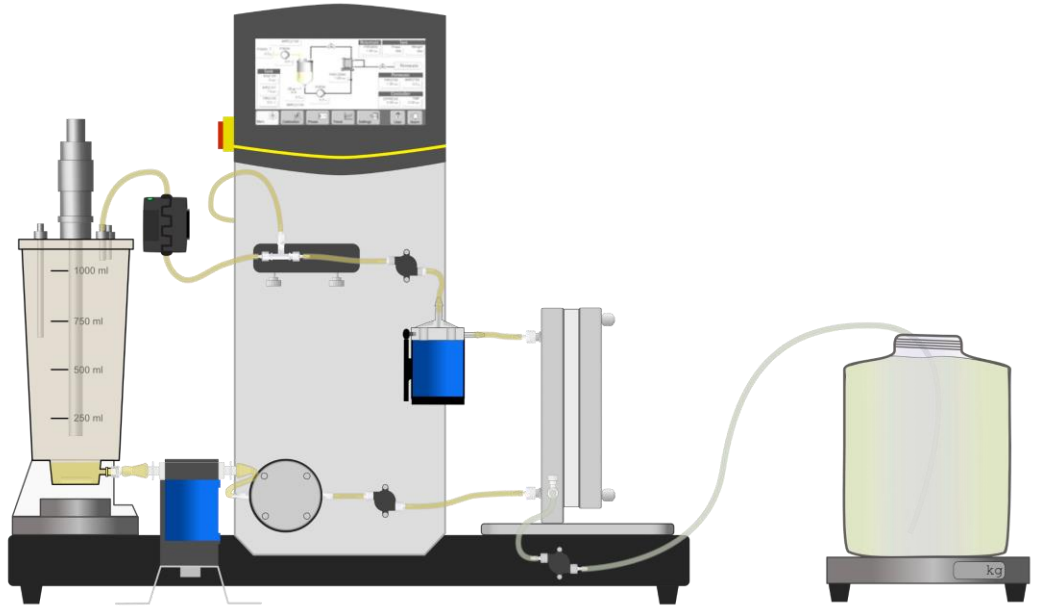
Process Highlights

Finish 2nd Ultrafiltration



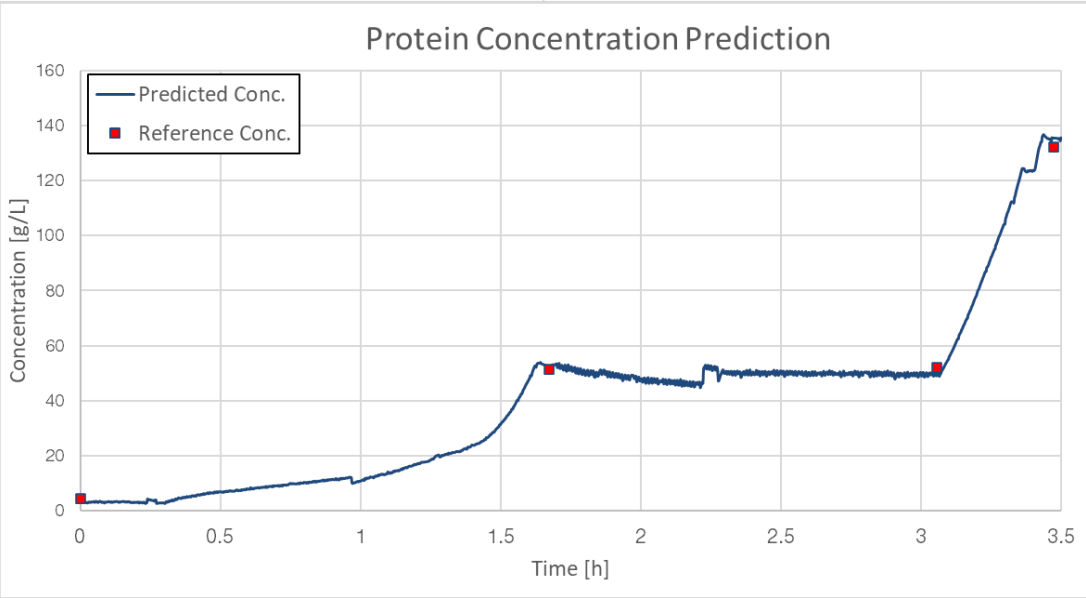


End Concentration (mg/mL)	140
End Volume (mL)	36
Duration (min)	25
Transmembrane Pressure (bar)	1.2

Online viscosity	Viscometer PAT	Levitronix	continuous data recording
Offline viscosity	microVISC	Rheosense	reference
Offline validated concentration	Solo VPE	C-Technologies, Repligen	reference
Offline concentration for monitoring	Nanophotometer	Implen	confirming volume changes and introducing phase change
SEC-HPLC	Vanquish Flex	Thermo Scientific	quality information

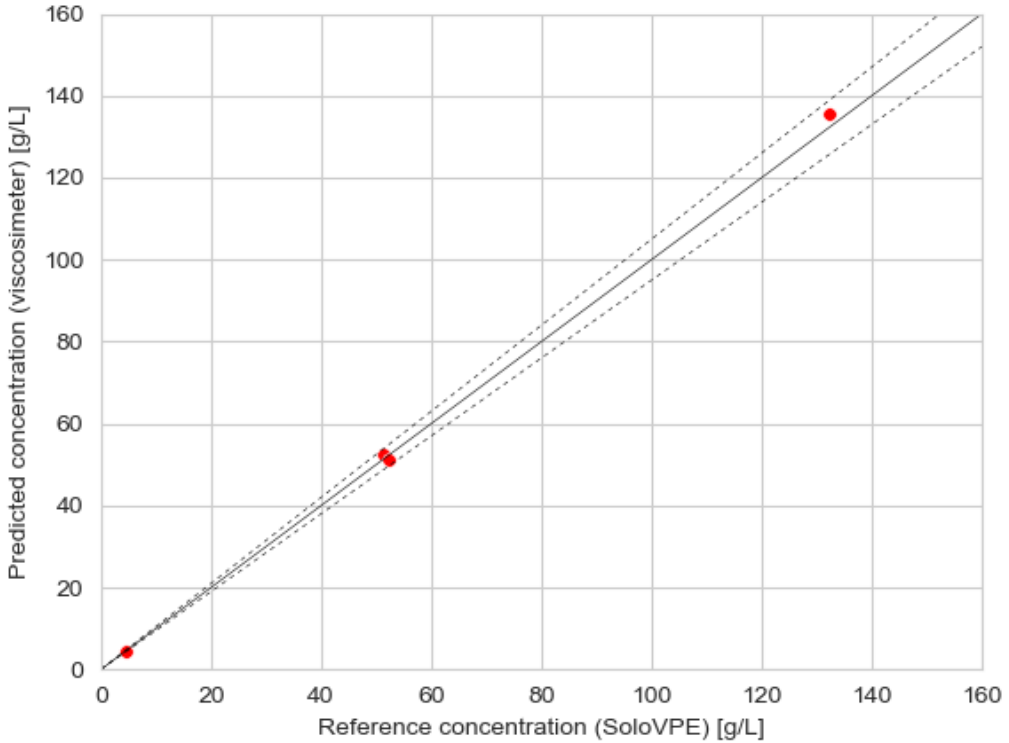
Monomer content of each sample during the process remained >96%, quality was not compromised.

Validation of calibration



- Four samples were taken during the TFF process to measure reference concentration value on Solo VPE, as a form of validation of the built prediction model.

- Good alignment between reference concentration and transformed viscosity data.
- The dashed lines are representing ±5% range from the setpoints in the process.



Reference [g/L]	Prediction [g/L]
4.4	4.4
51.4	52.6
52.1	51.0
132.3	135.4

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Outlook and Applicability

- Better control
- Cheap
- Automated
- Reliable results
- Mechanistic, hybrid, or statistical modelling
- Process knowledge
- Opportunities to compare conditions
- Less human interaction with the system setup
- Trouble shooting

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Acknowledgments

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FBIC team (Jessikah Swasbrook, Analytical Scientist)

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Thank you!