Smart Bioprocess Development Grand Challenge

Webinar May 2024

Digital Technologies in Bioprocess Development: Accelerating Medicines to Market

Agenda

10:00 – Owen IUK - Introduction

10:05 – Elaine - Introduction to CPI, and Smart Bioprocessing Grand Challenge – 10 minutes

10:15 – Lukas – structure of project, digital infrastructure, MMIC Data Institute – 10 minutes

10:25 – Sean – analytical platforms, example data, experimental automation (closed loop) – 10 minutes

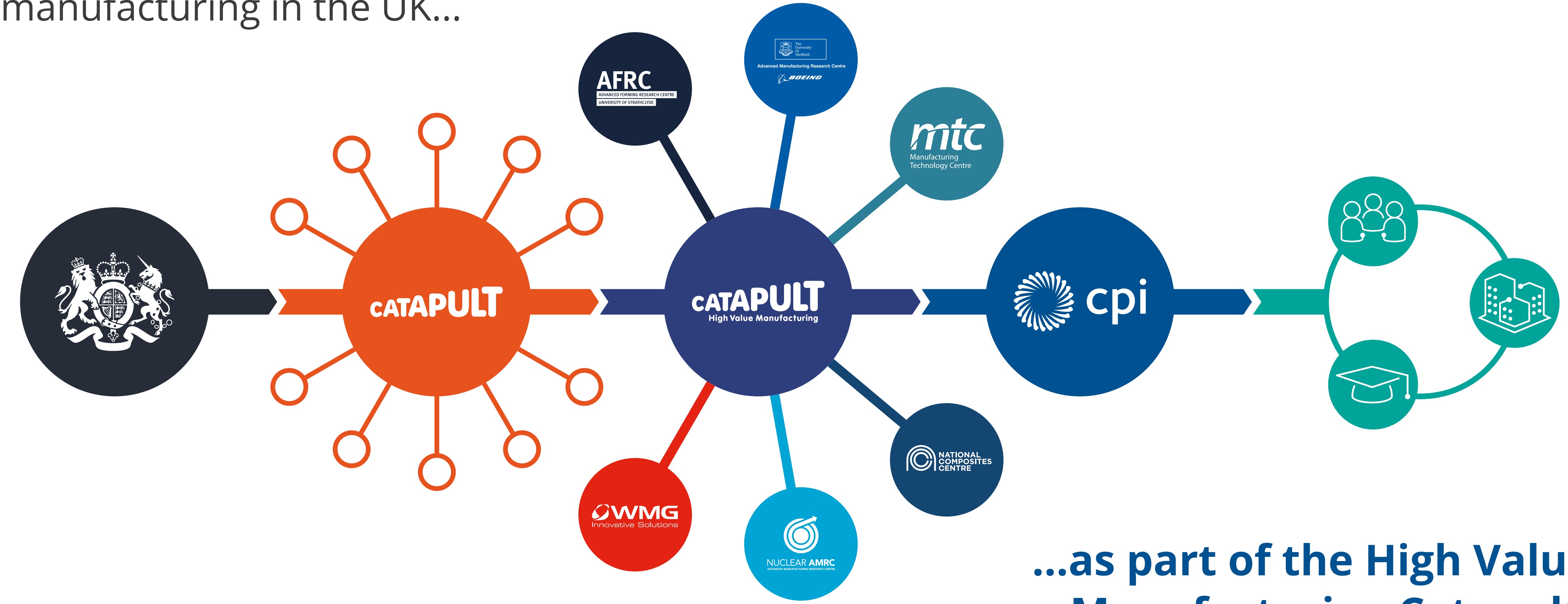
10:35 – Alessandro Butte – Analysis and modelling of LC-MS data – 10 minutes

10:45 – Q&A – 10 minutes

10:55 – Close

We help companies to develop, prove, scale-up and commercialise new products and processes

Supporting the growth and development of advanced manufacturing in the UK…



…as part of the High Value Manufacturing Catapult

We help deliver, de-risk and accelerate...

...your concepts into successful products

...at our national centres of excellence across the United Kingdom

Biologics

Medicines Manufacturing

Formulation

Biotechnology

Electronics

Photonics

The Smart Bioprocess Development project is a collaboration between

- CPI
- DataHow
- Waters
- The Earlham Institute

Problem Statement

Process Development is slow and very expensive.

- Typical process development can take months or years, increasing drug costs and time-to-market.

Difficult to use learnings from one process or product to inform new ones

- Need to “start from scratch”, or at least a low baseline.

Model-driven process development offers reductions in # of experiments but is currently limited in use.

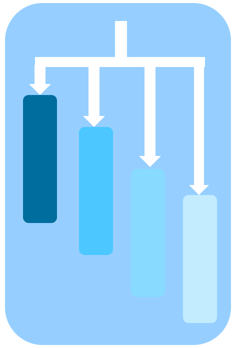
- Hampered by limitations of transferability and data.

No-one has enough suitable data

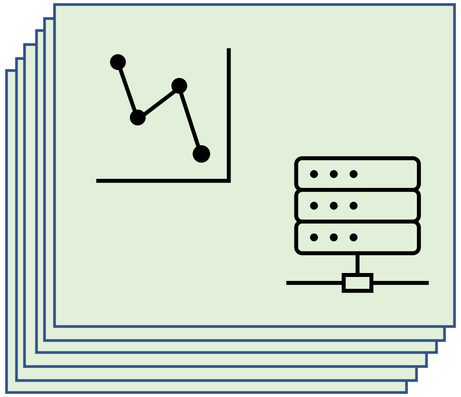
- No structured dataset, analytics not sufficient
- Datasets not rich or varied enough for transfer learning

Smart Bioprocess Development Vision

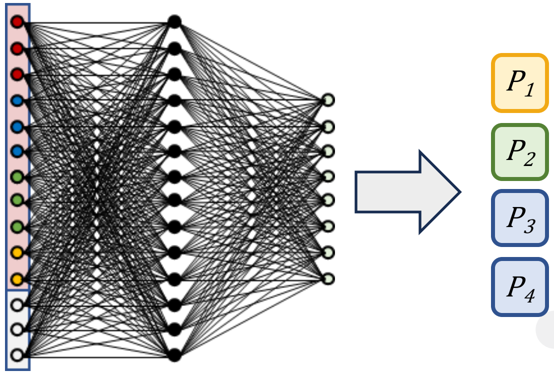
Instead of DoE-based process...



Use **powerful analytics** to characterise a sample from a new process



Characterisation is compared to **large dataset** of previous experiments from many processes

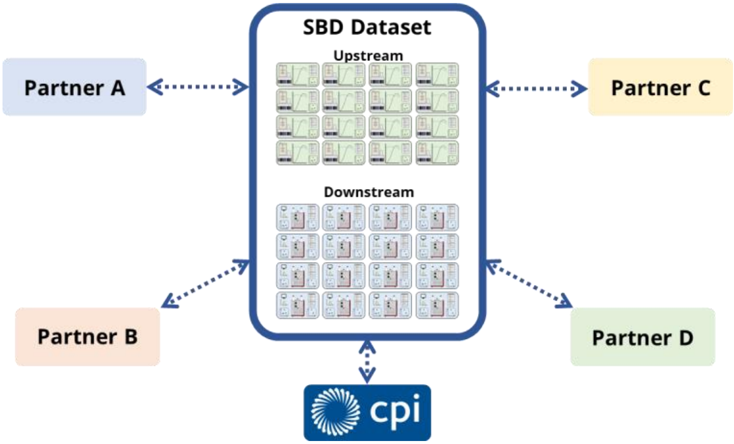


Predictive models give optimised process and process parameters

How do we get there?

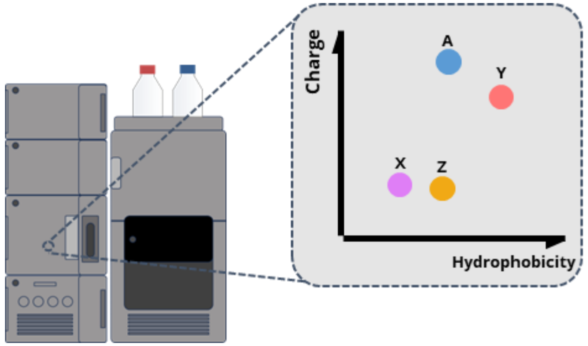
Rethinking Datasets

How do we structure and share data?



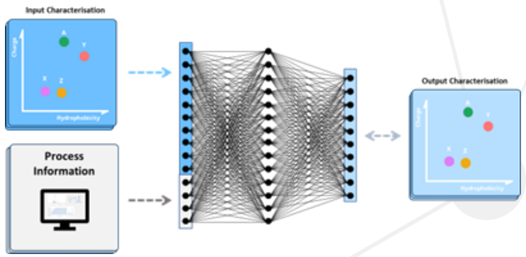
Better Development Tools

How do we improve data we are taking?



Smarter Modelling

How do we improve understanding and prediction?



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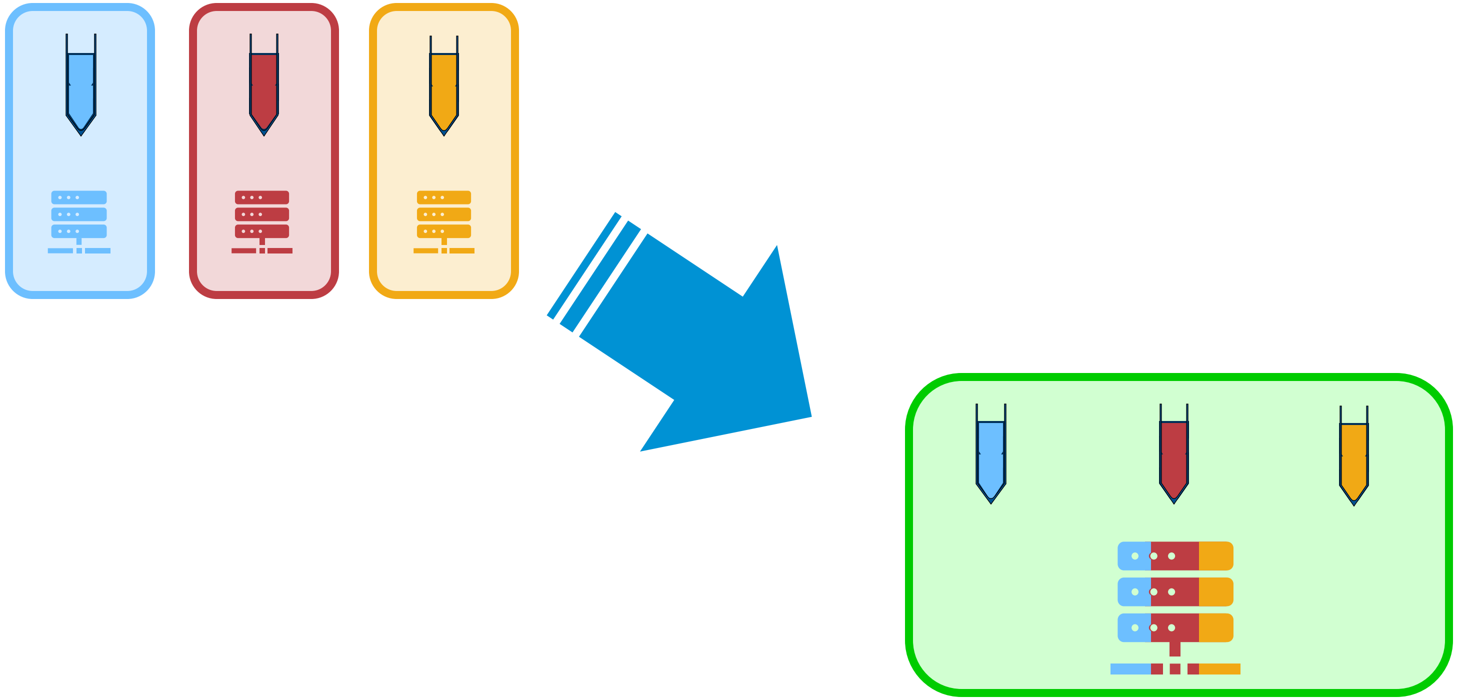
Rethinking Datasets

How do we structure and share data?

Process Specific

One process
at a time



Process Agnostic

Combines
Many
Processes

How do we get there?

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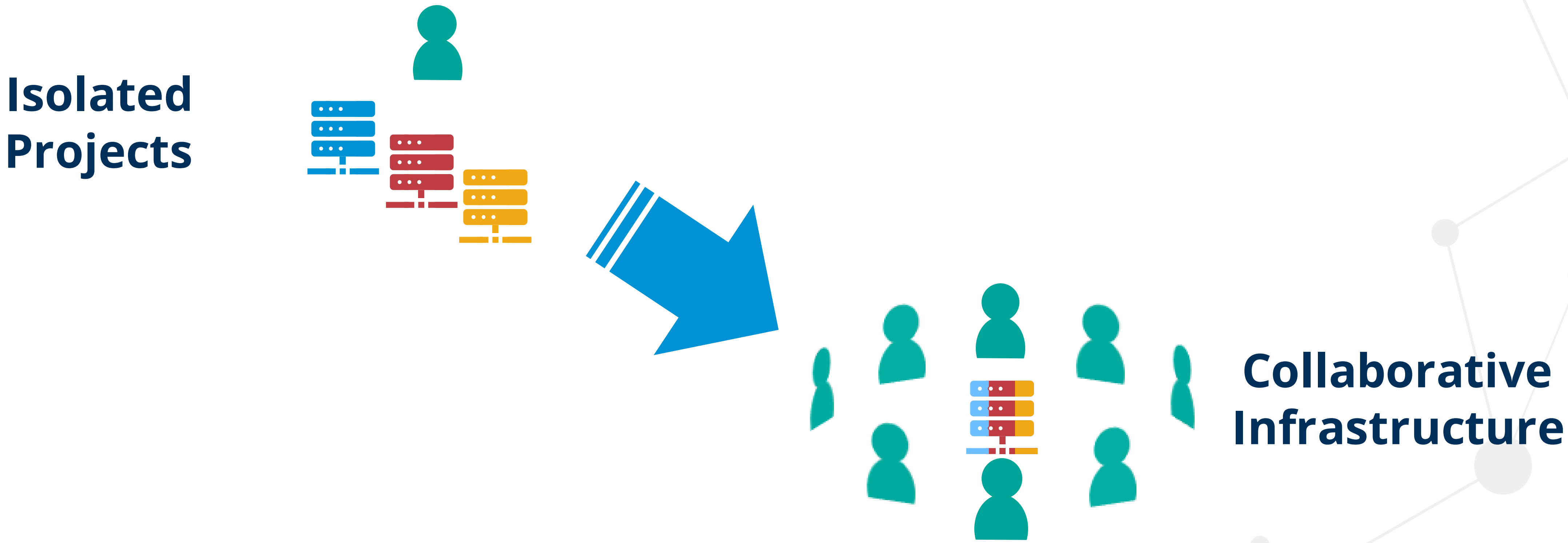
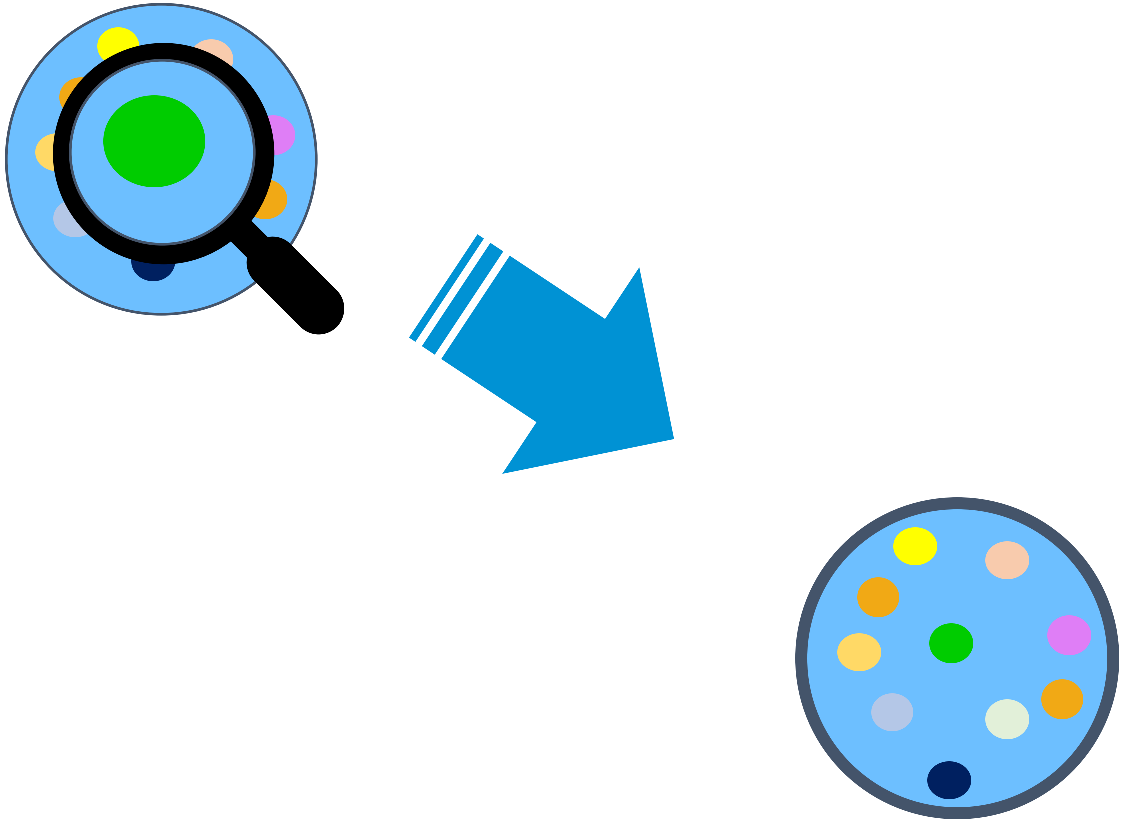


How do we get there?

Better Development Tools

How do we improve and utilise data we are taking?

Product Focused Analytics



Data Rich Analytics

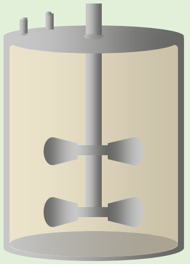
Capture Product and Impurity Behaviour

How do we get there?

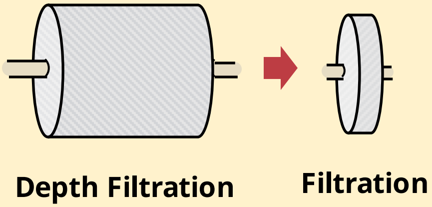
Data-Rich Analytics

3 Key Areas

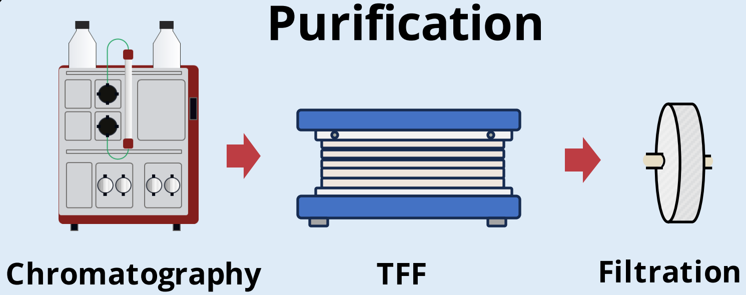
Upstream



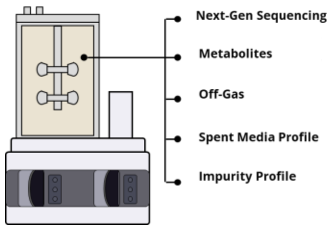
Clarification



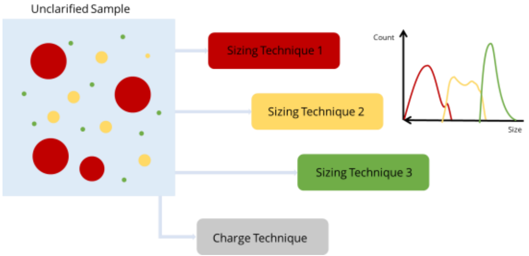
Purification



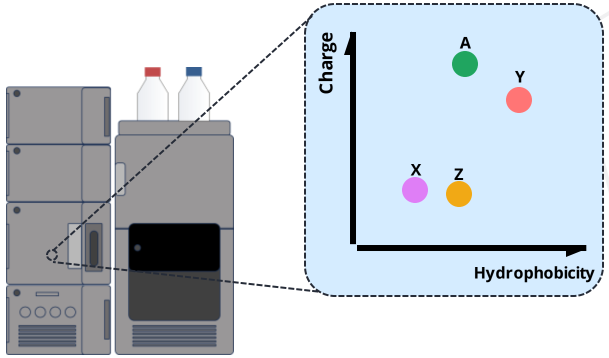
3 Analytical Platforms



AMBR-Based
Upstream Development Platform



Size & Charge-based
Clarification Development Platform



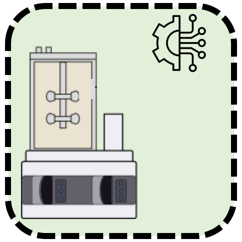
LC/MS Based
Purification Development Platform

How do we get there?

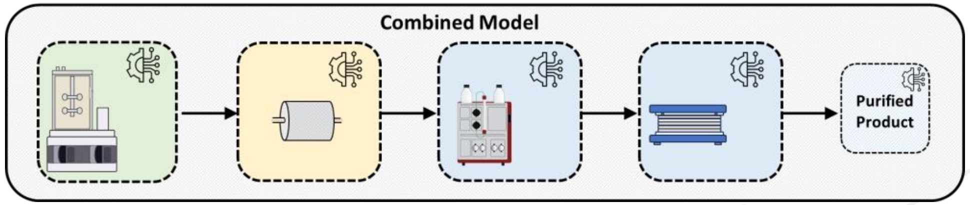
Smarter Modelling

How do we improve understanding and prediction?

Individual & Simplistic Modelling

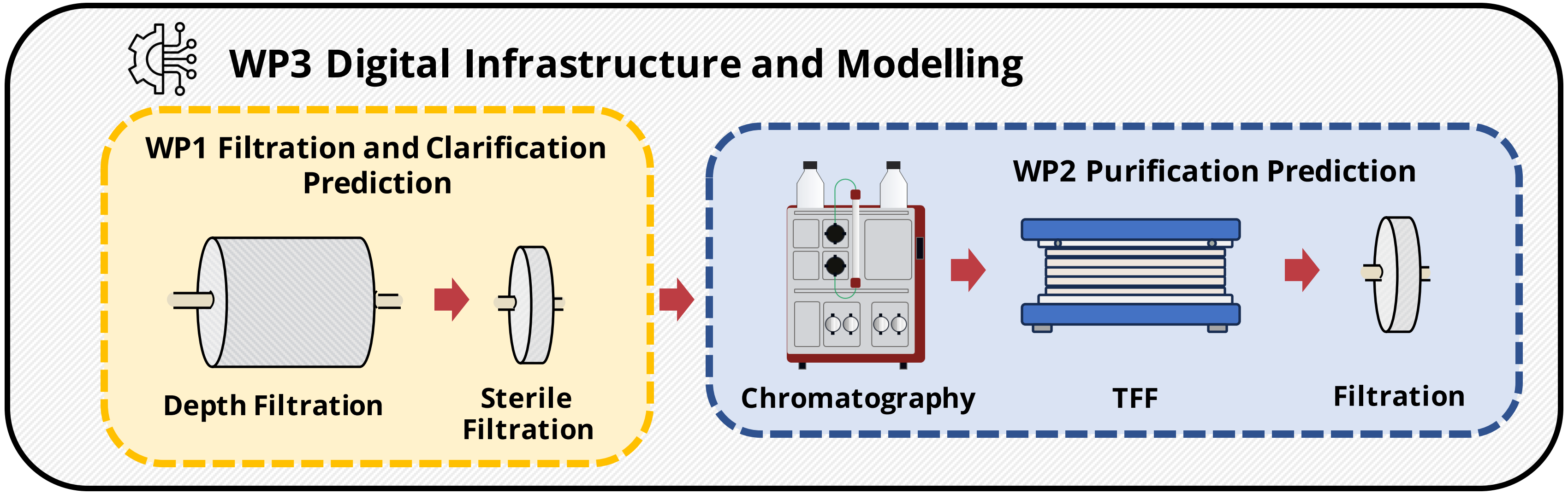


Holistic & Hybrid Models



Proof of Concept/Ongoing Work

Proof of Concept Study Funded by **Innovate UK** to explore concept for clarification and purification prediction, and to develop the Scope and Consortium for the full Grand Challenge.



PoC funded May 2023 – October 2024

Working with: **DataHow** as a hybrid modelling partner

Earlham Institute for Next Gen Sequencing data

Waters as LC/MS Partner

Rethinking Datasets

Data and digital infrastructure

Lukas Kuerten

cpi

www.uk-cpi.com

Smart Bioprocess Development Vision

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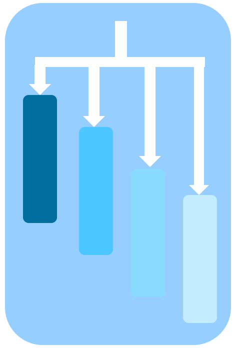

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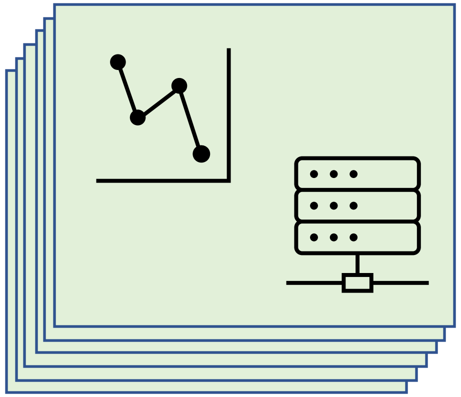

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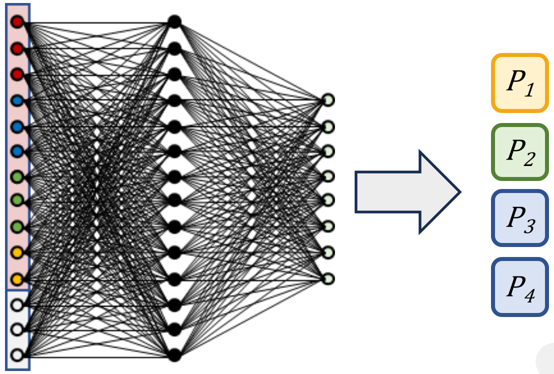
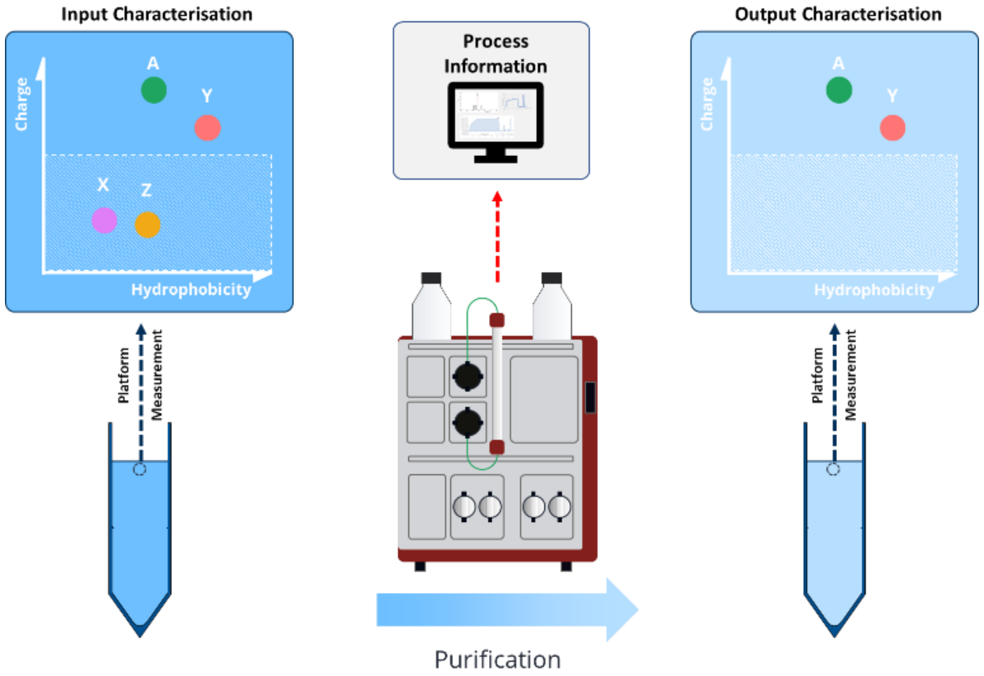


Predictive models give optimised process and process parameters

Modelling – Chromatography Example

Use LC/MS as a platform analytic for purification experiments.



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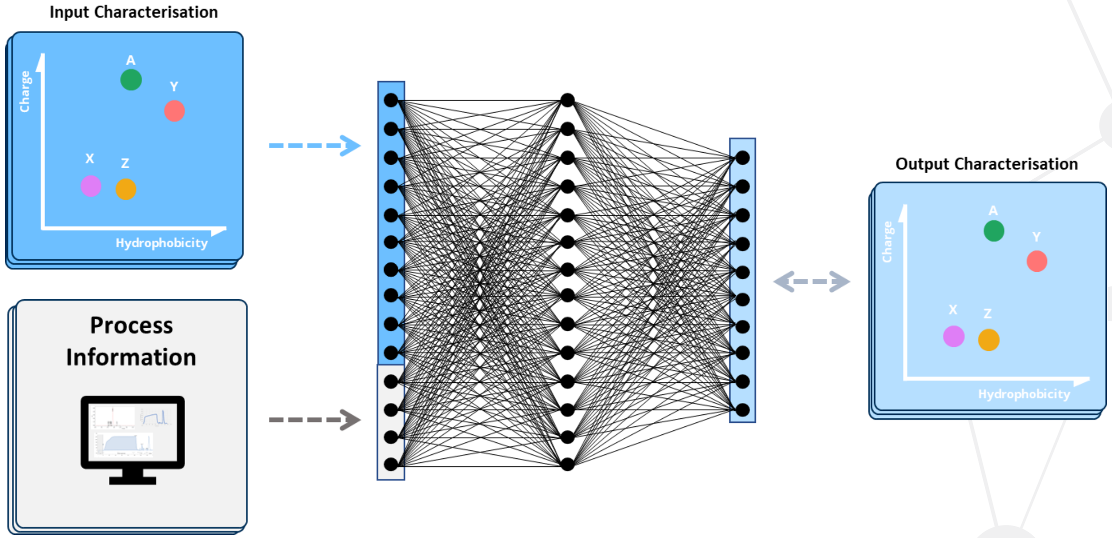
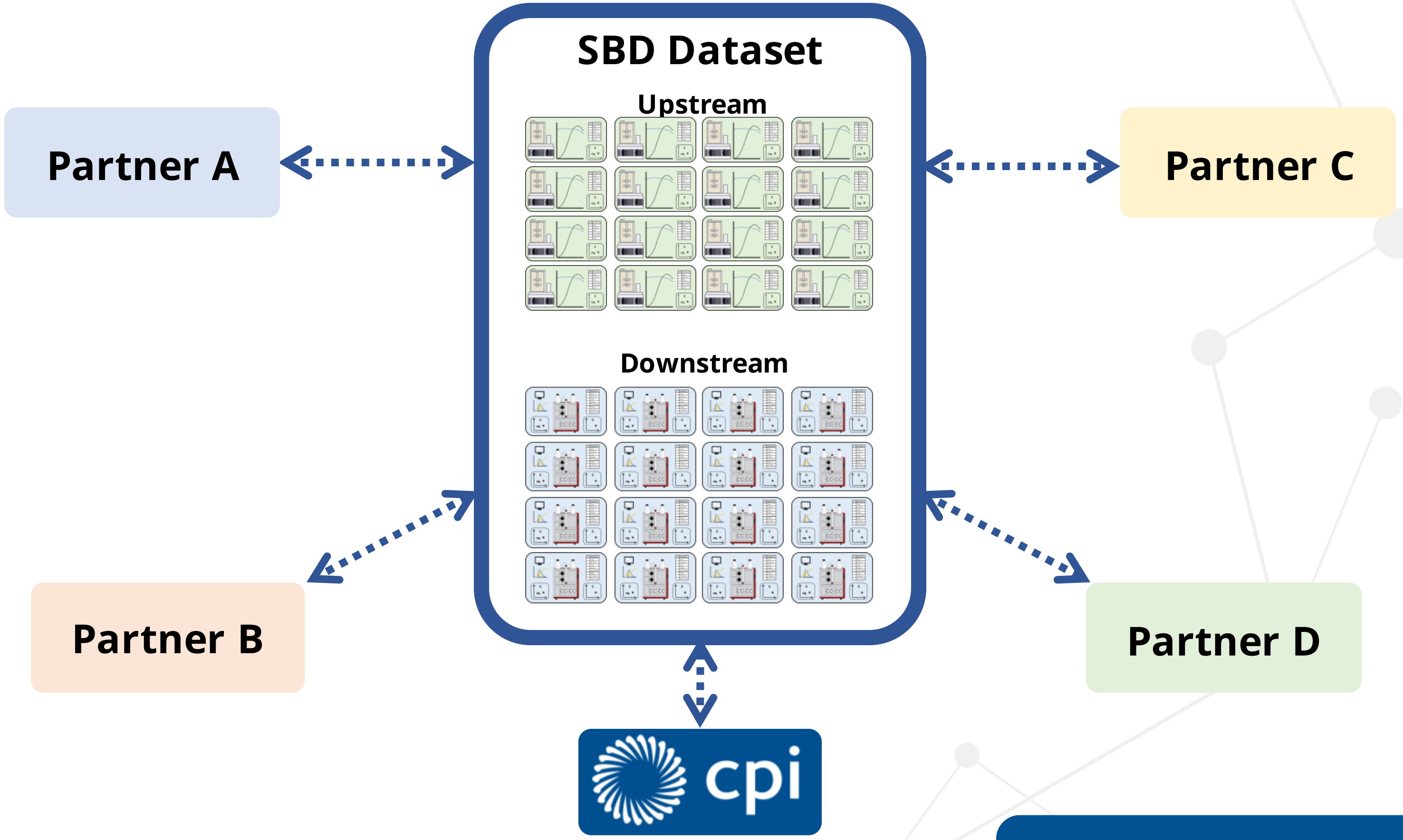


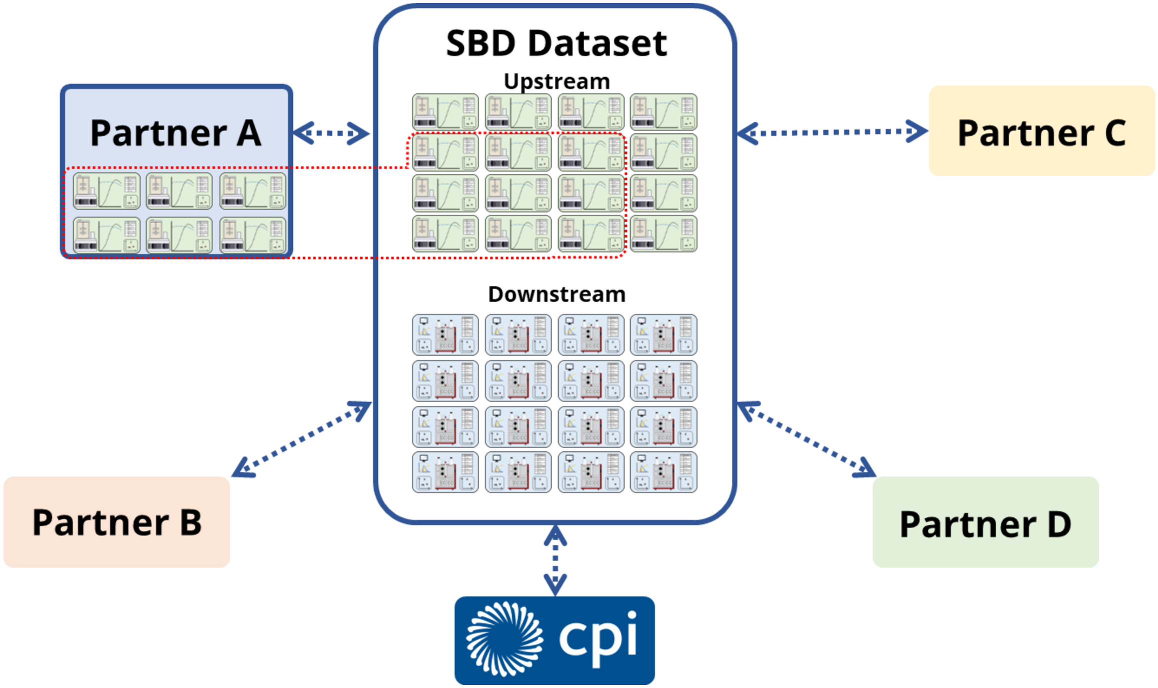
Data Institute Approach

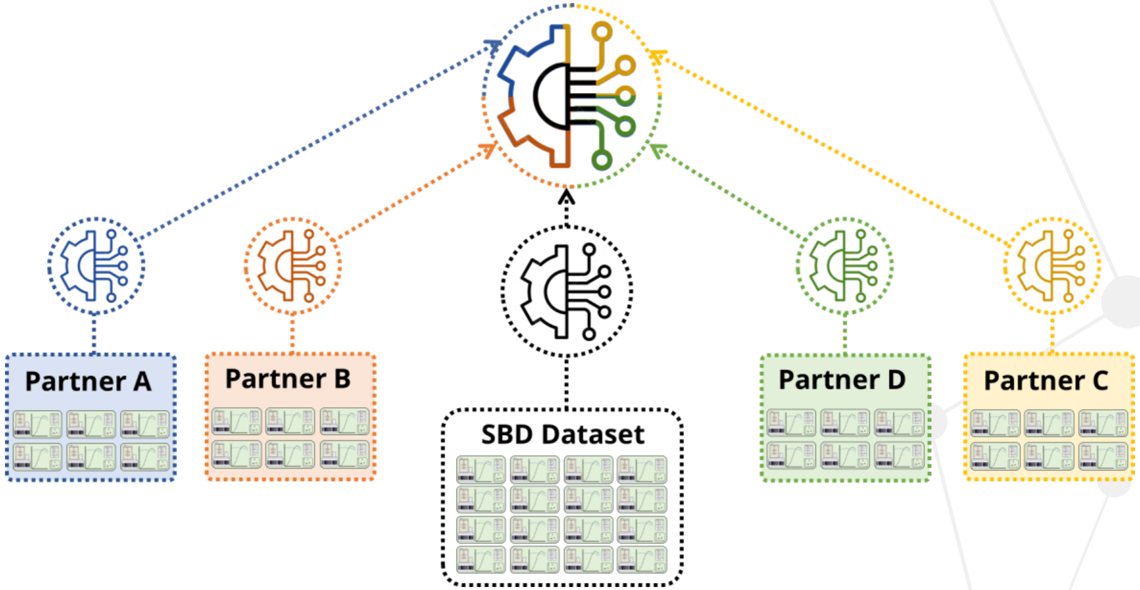
- **Scalable, Cloud-Based infrastructure** for data security and future growth. Working with AWS to design concept.
- **Large, analytically rich & structured core dataset** accessible to all partners to provide orientation + structure.
- Partners can contribute data and use as modelling platform.



Data Institute Approach

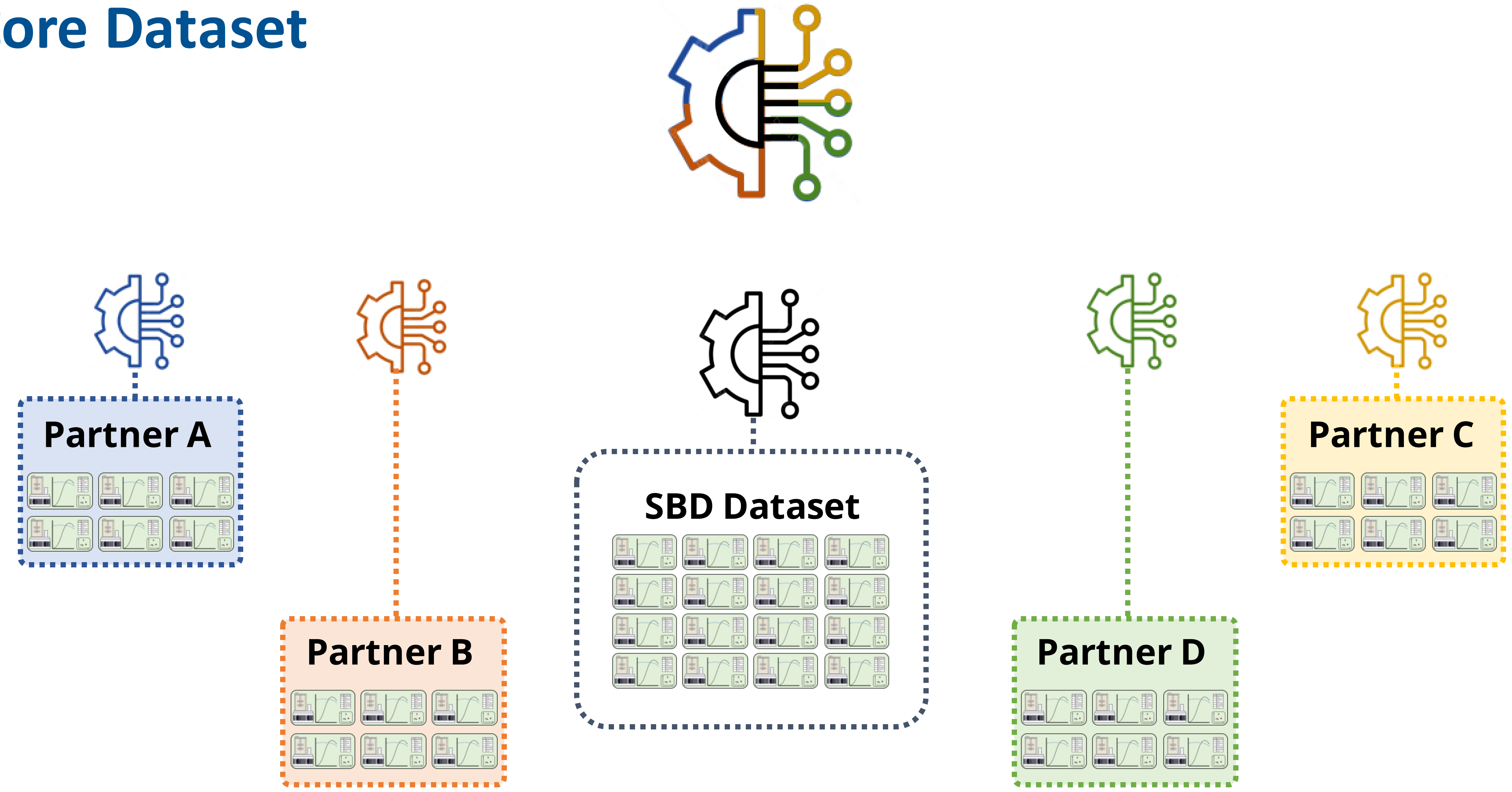
Partners can utilise institute for model building with own data



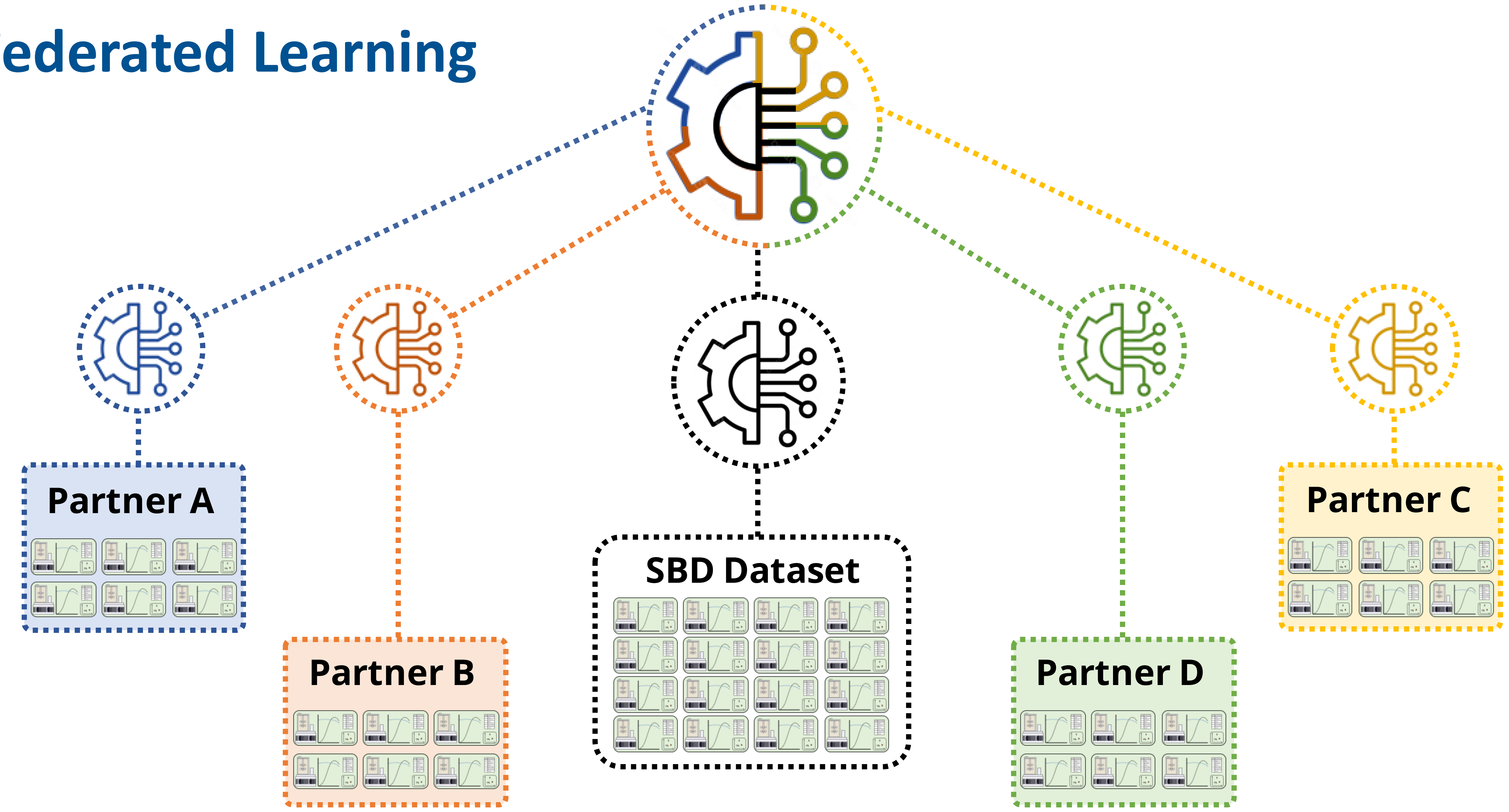


Full cross-organisation model capability achieved by federated learning.

Core Dataset



Federated Learning



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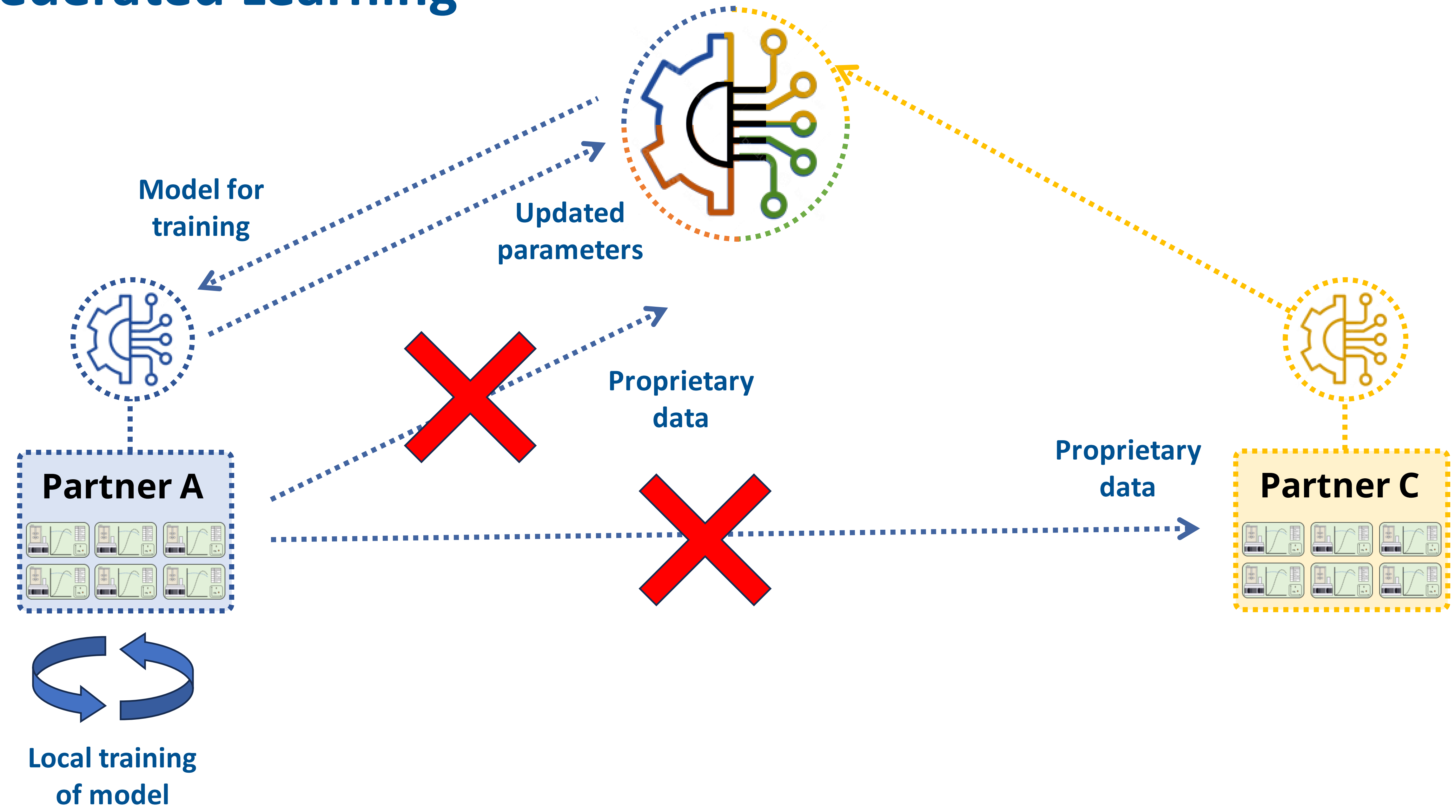
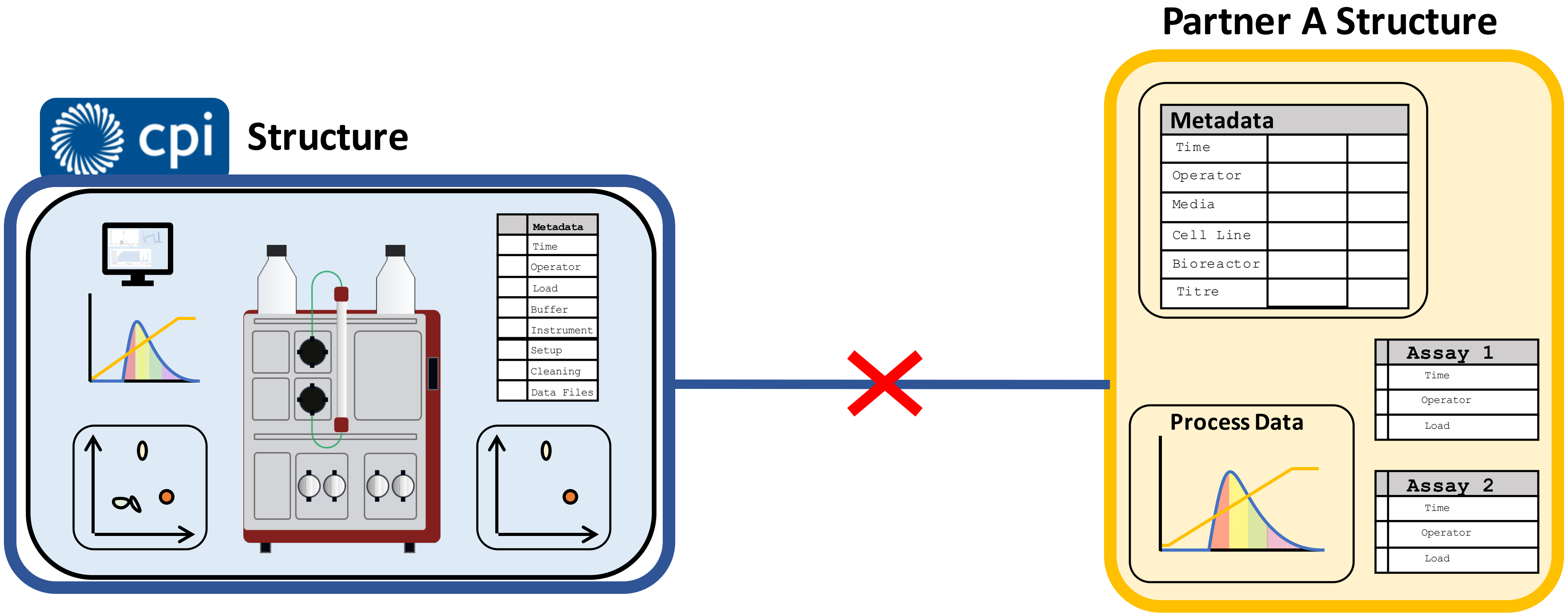


Flexible Data Ontology

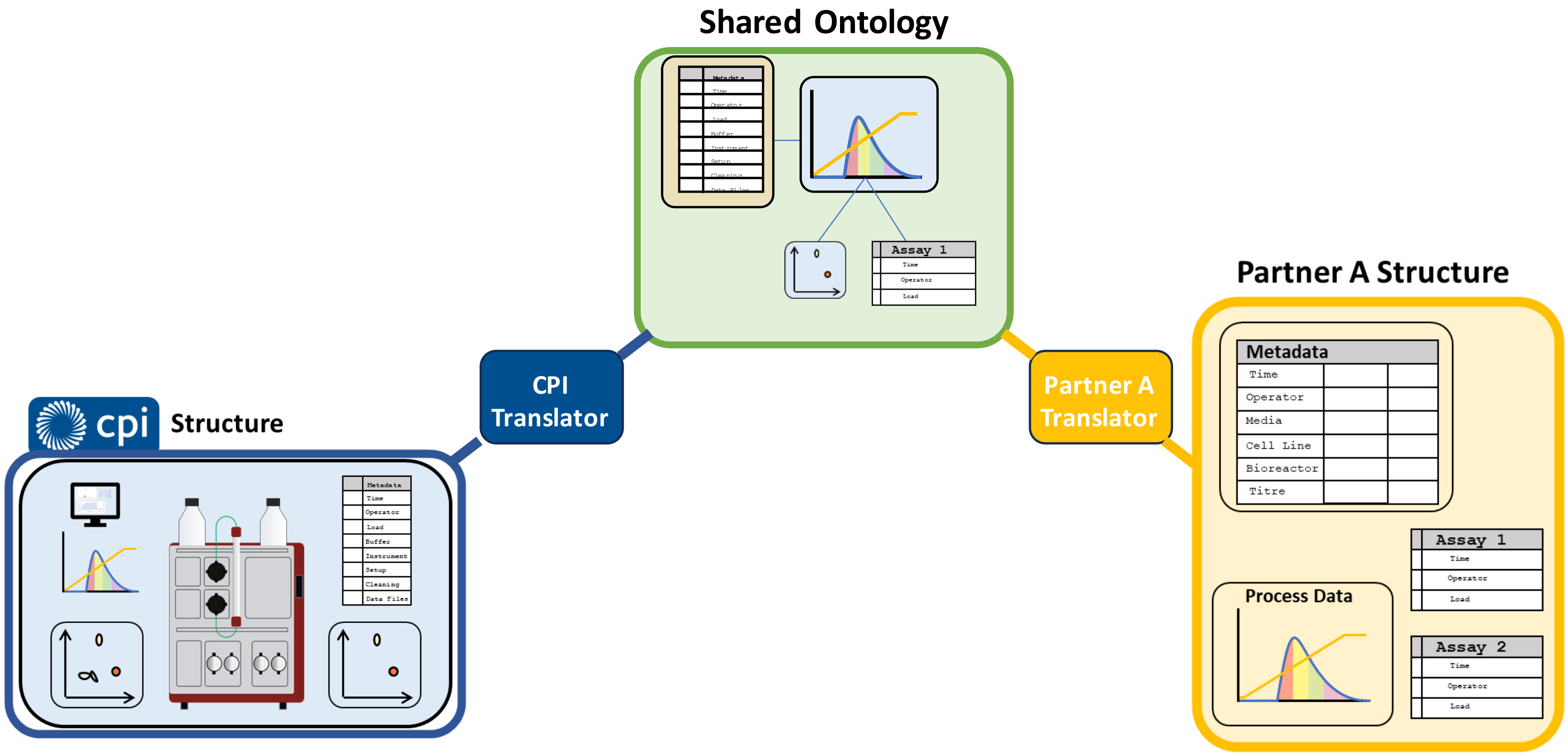
Differences in data structure across and between organisations makes data sharing & federated learning challenging.



Flexible Data Ontology

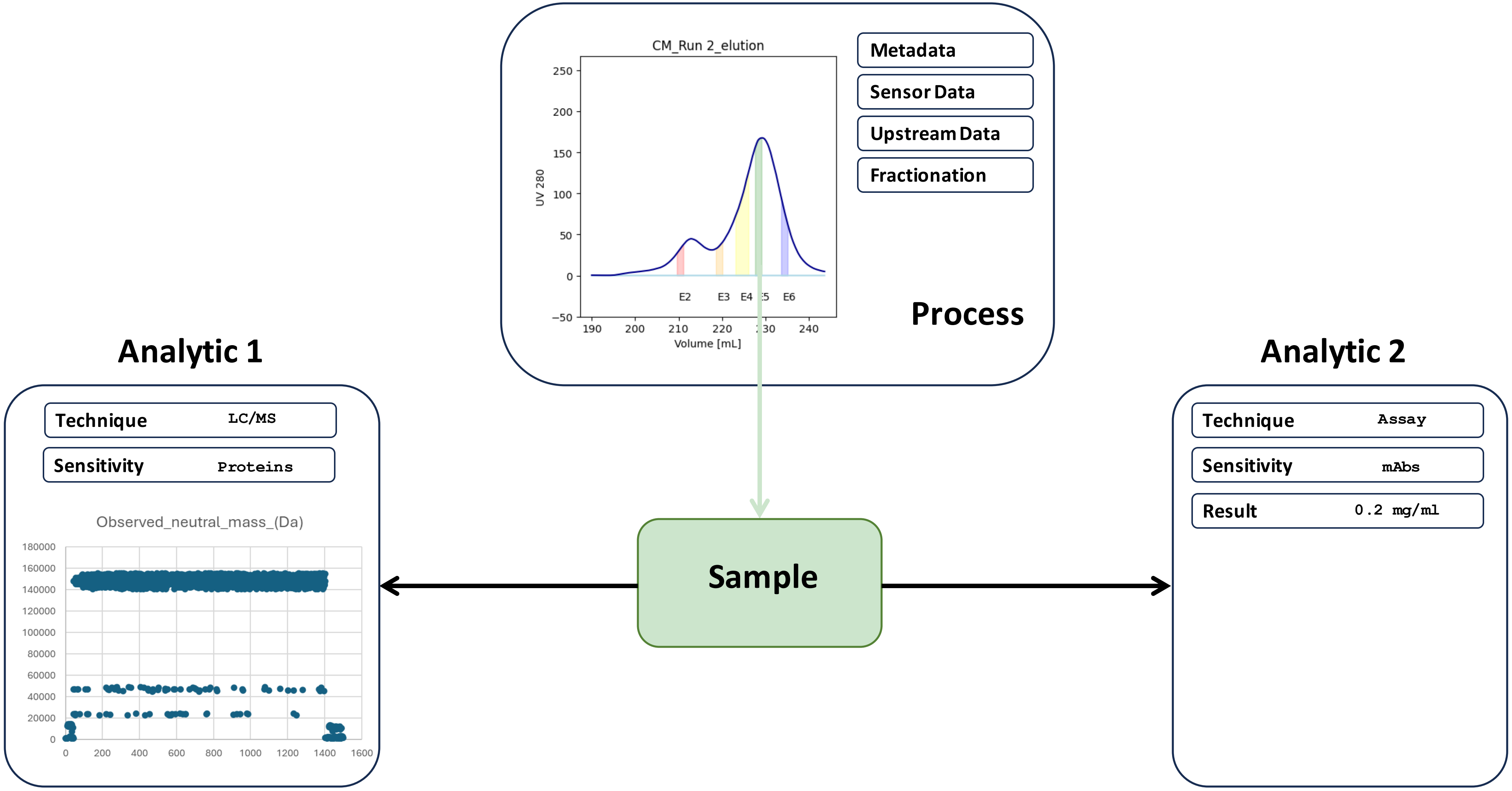
Build **shared language & structure** to describe relevant processes and analytical results, including their sensitivities.

Look to align with **NIIMBL** Bioprocess Manufacturing ontology



Allow greater analytical flexibility & use of historical data

Flexible Data Ontology - Example



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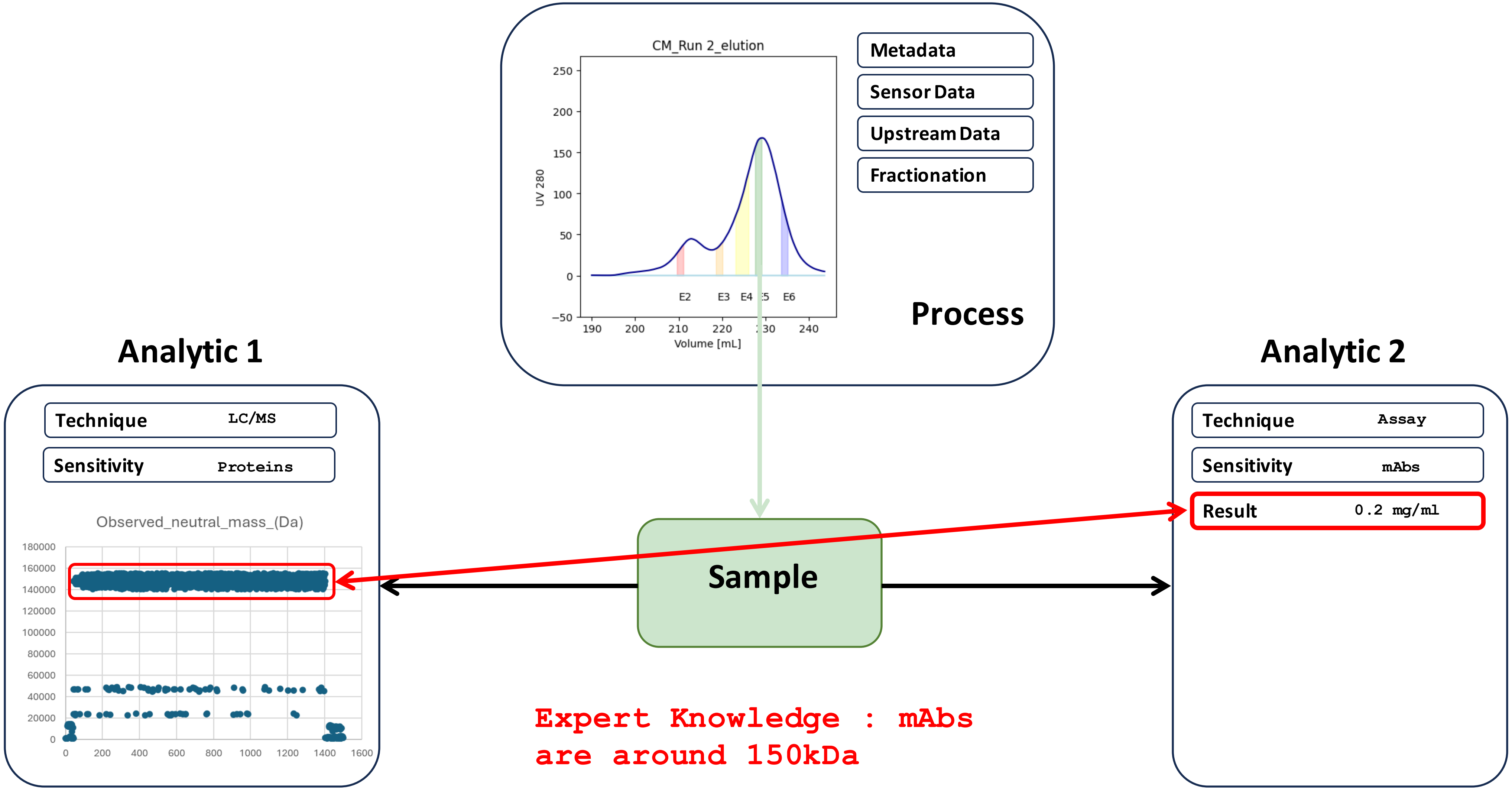
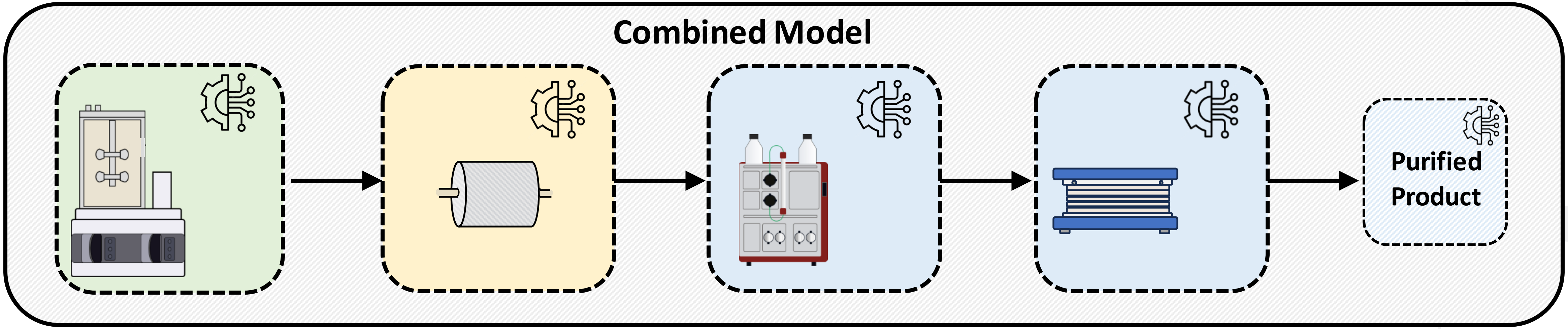


Combining Models



Analytics and models designed to tie together to provide **holistic process modelling**

Connect into **BioSolve** to provide economic & environmental optimisation

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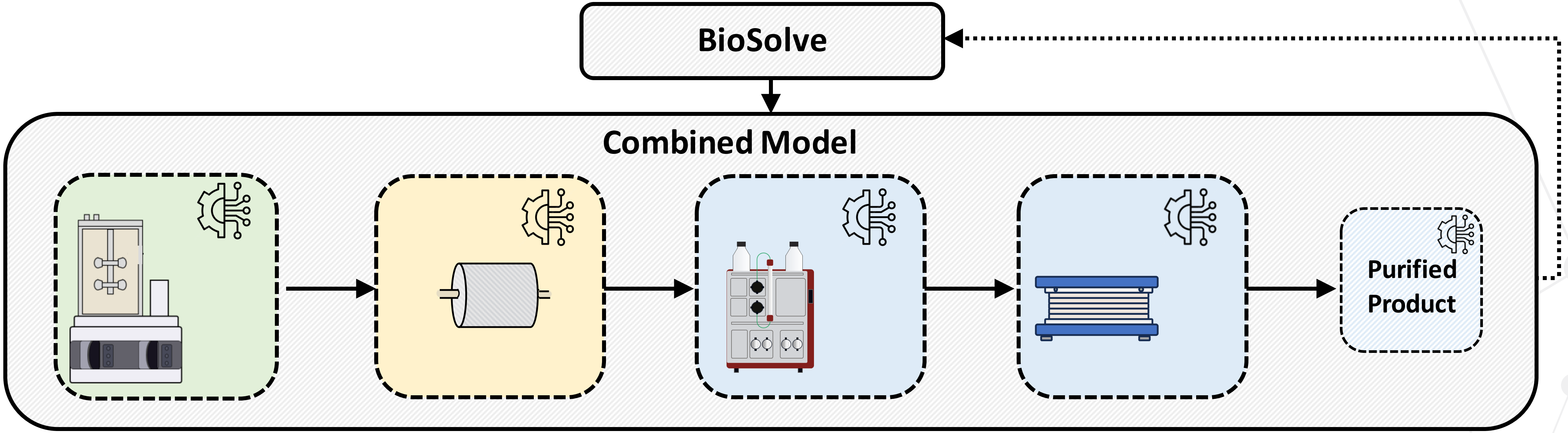
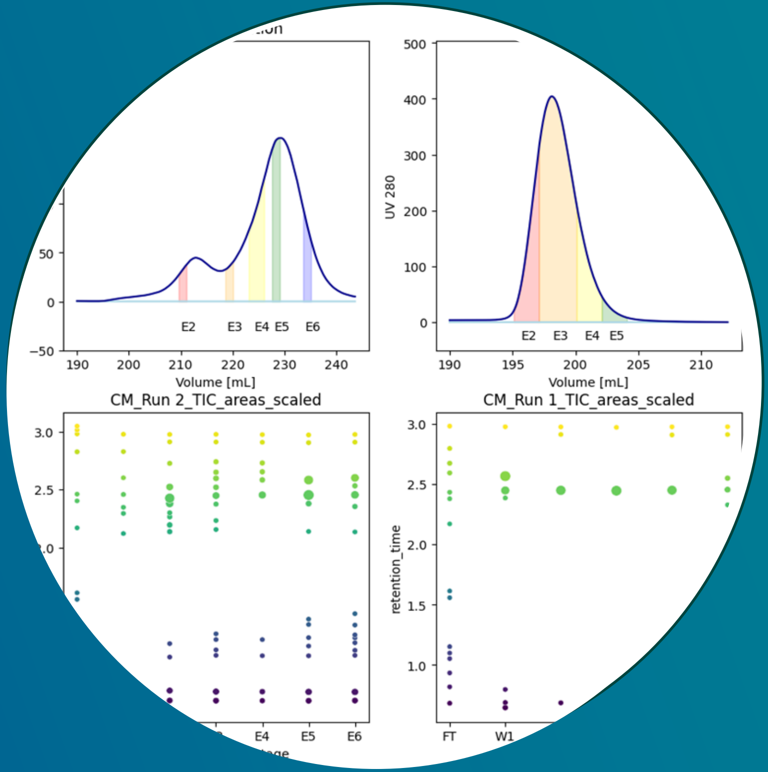


Platforms and models designed to tie together to provide **holistic process modelling**

Connect into **BioSolve** to provide economic & environmental optimisation

Better Development Tools

Sean Ruane

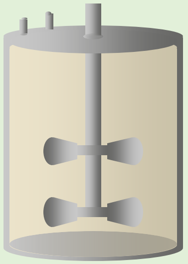


How do we get there?

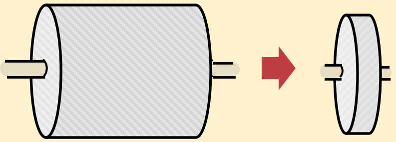
Data-Rich Analytics

3 Key Areas

Upstream

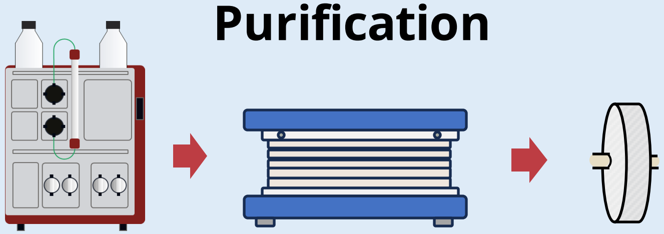


Clarification



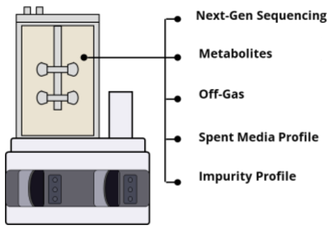
Depth Filtration Filtration

Purification



Chromatography TFF Filtration

3 Analytical Platforms



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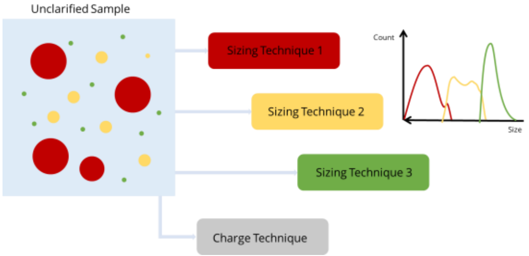
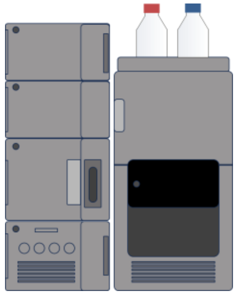
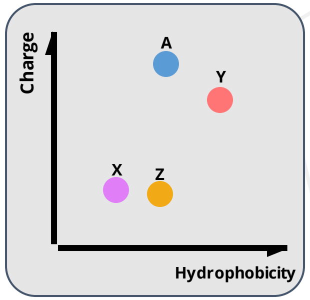
Upstream Development Platform



Size & Charge-based
Clarification Development Platform





LC/MS Based
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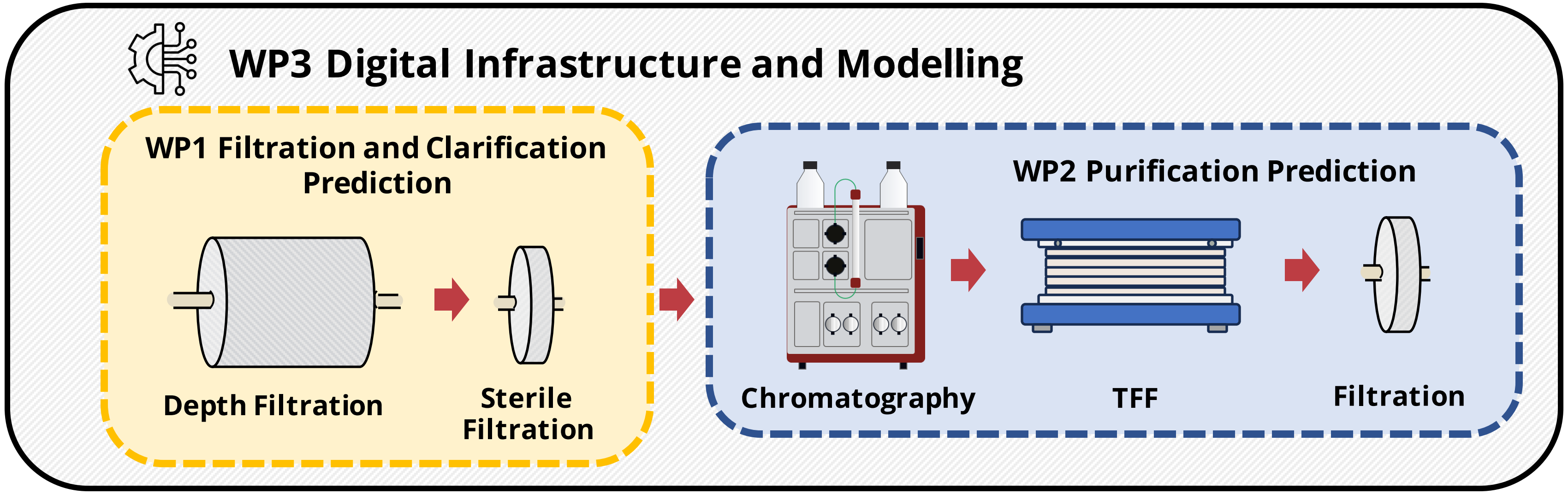

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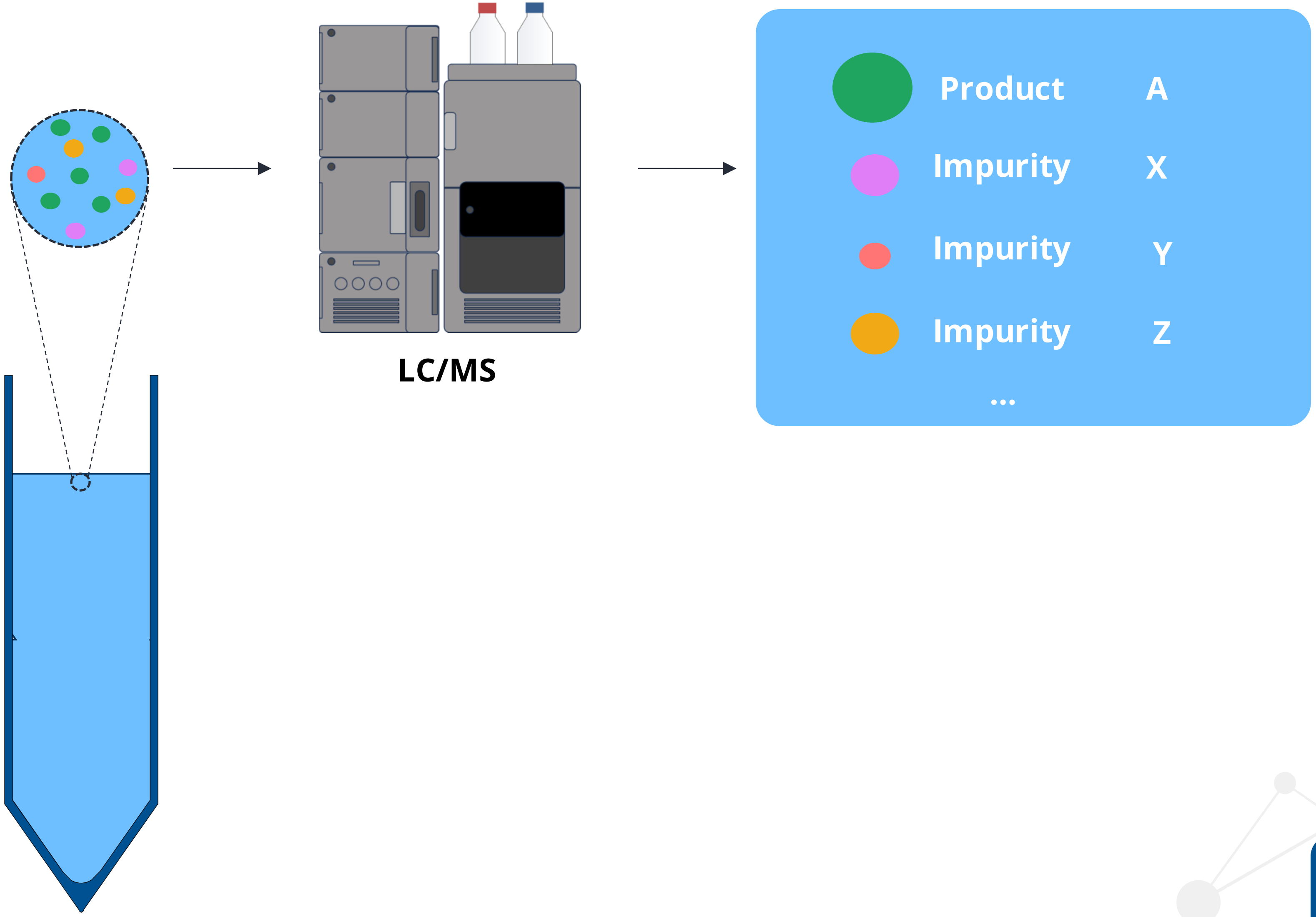

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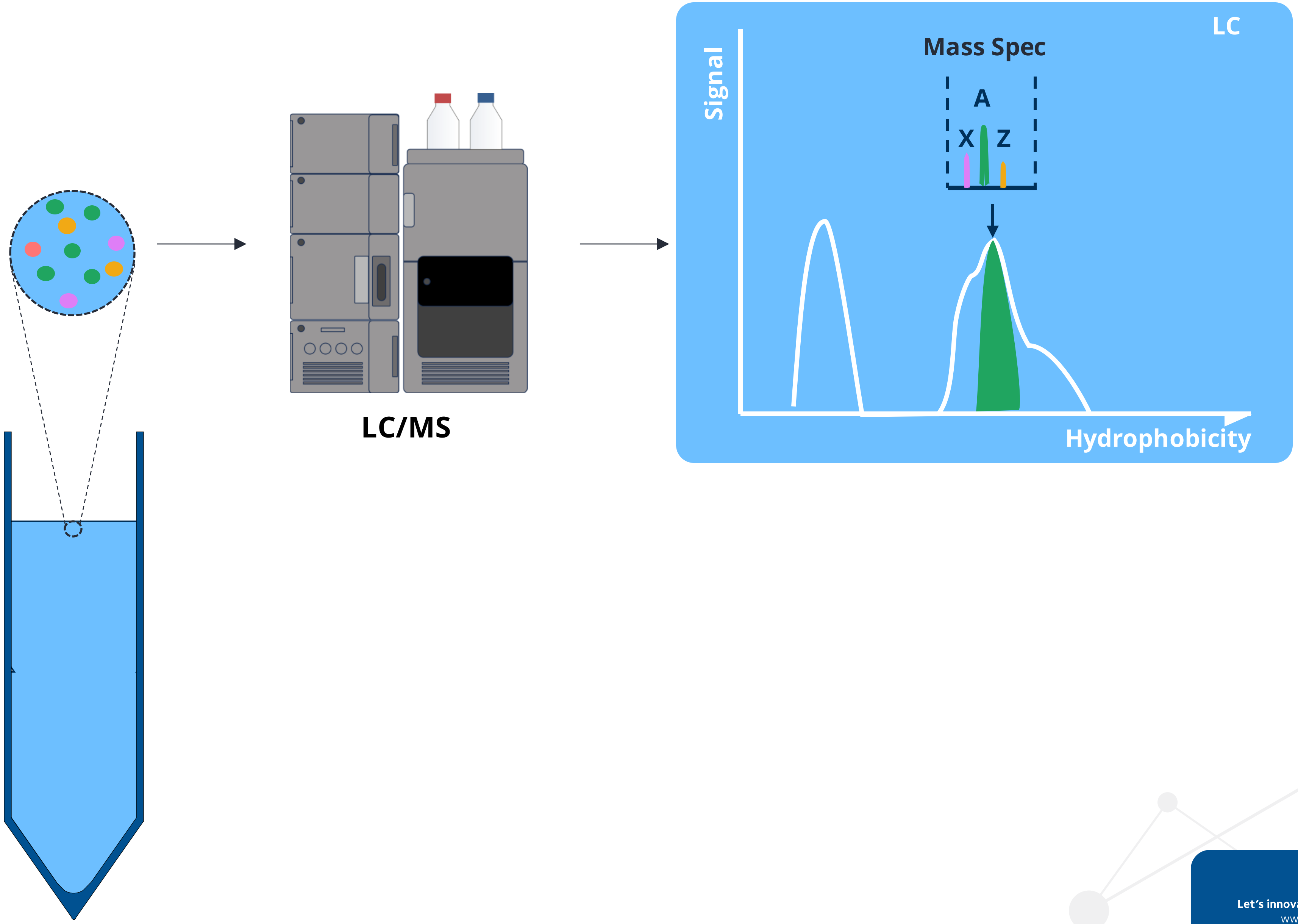

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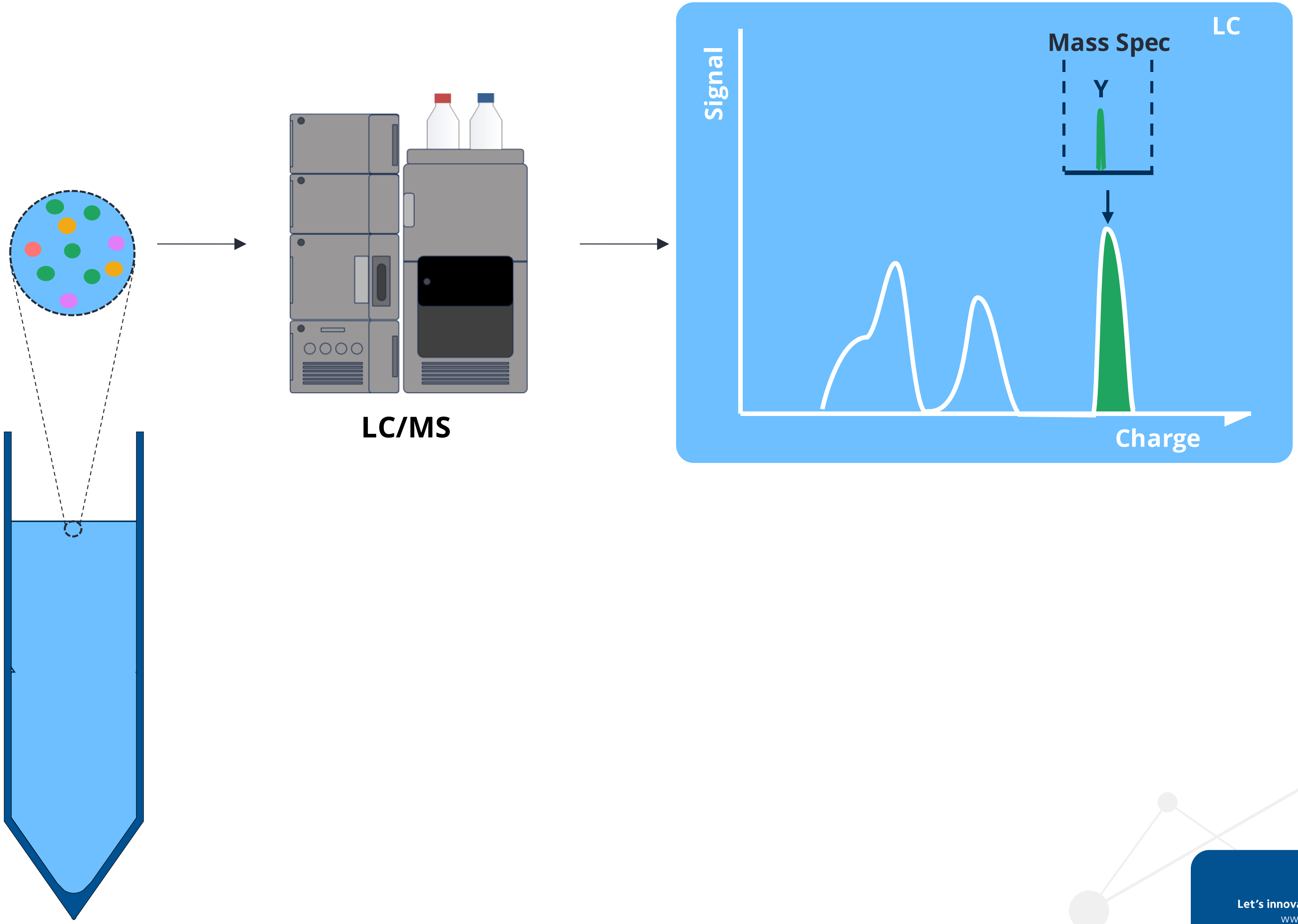

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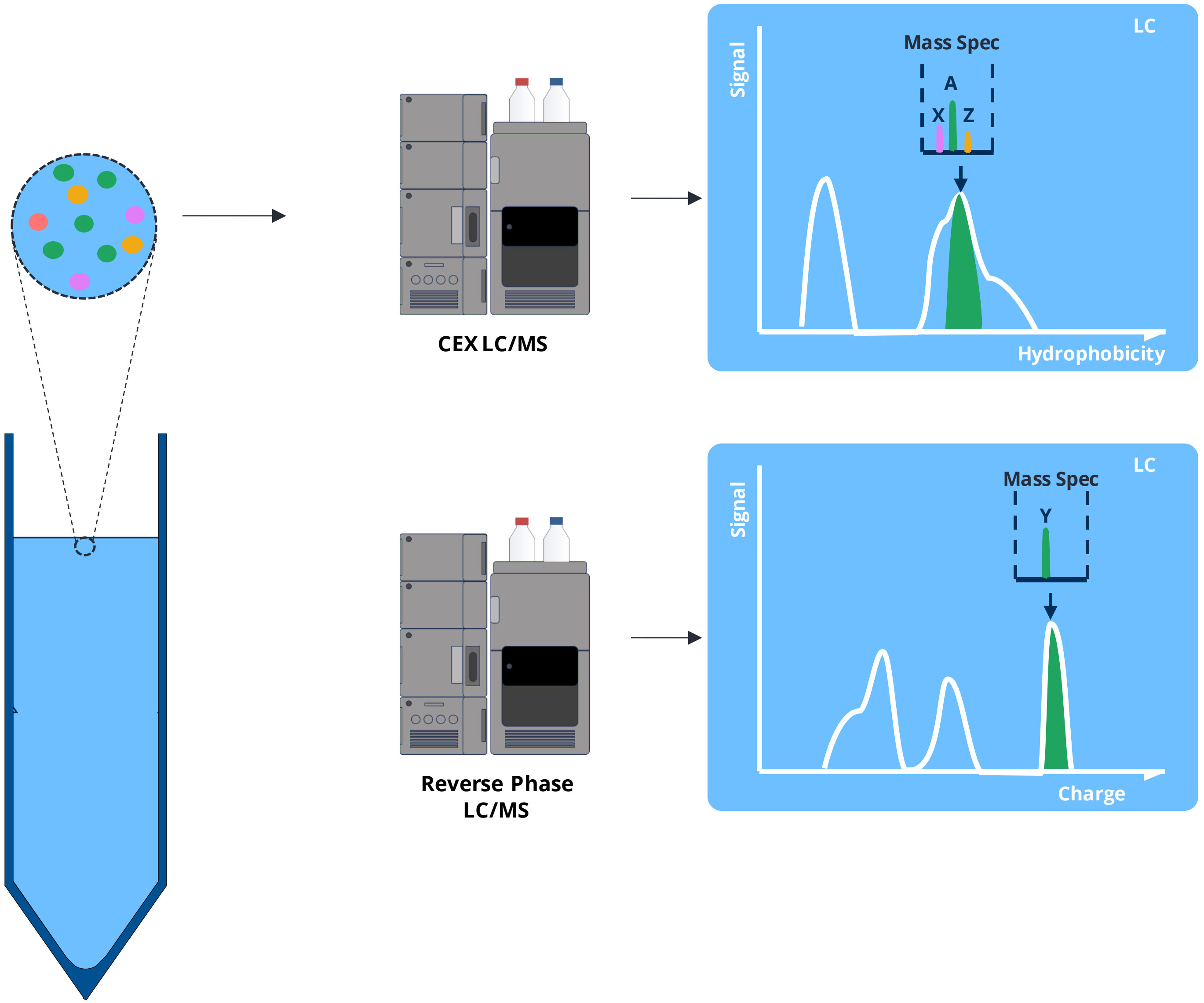

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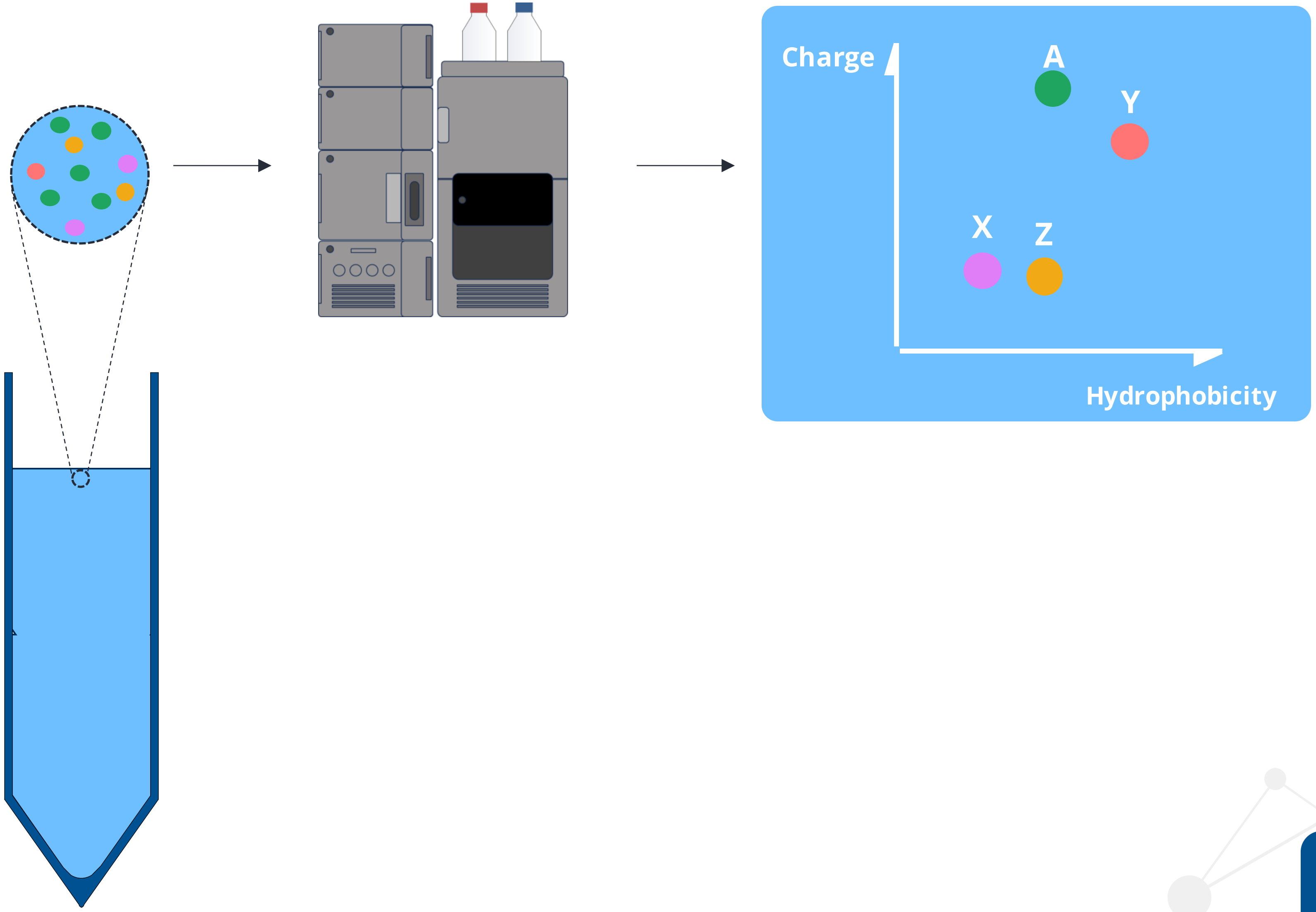

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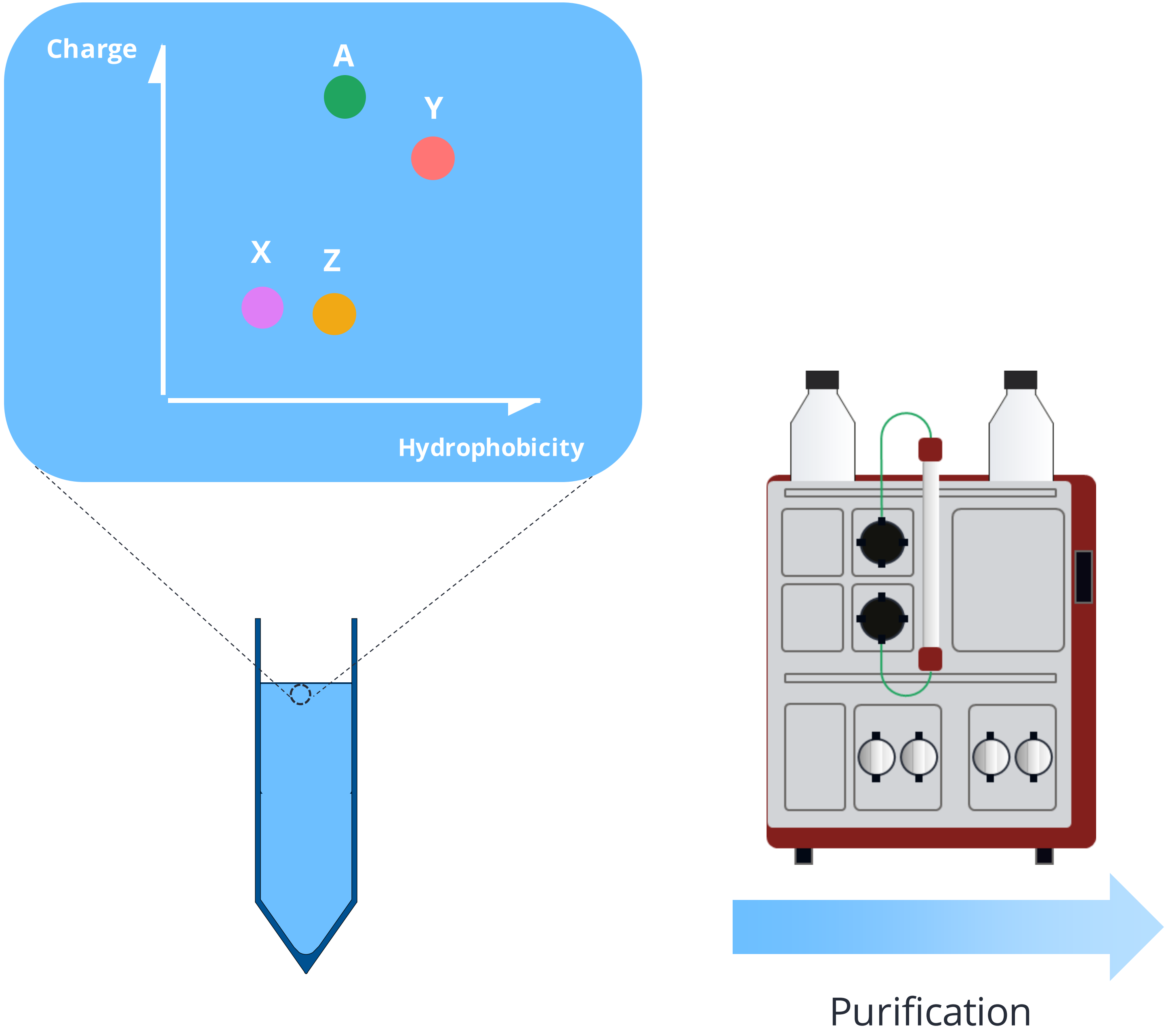

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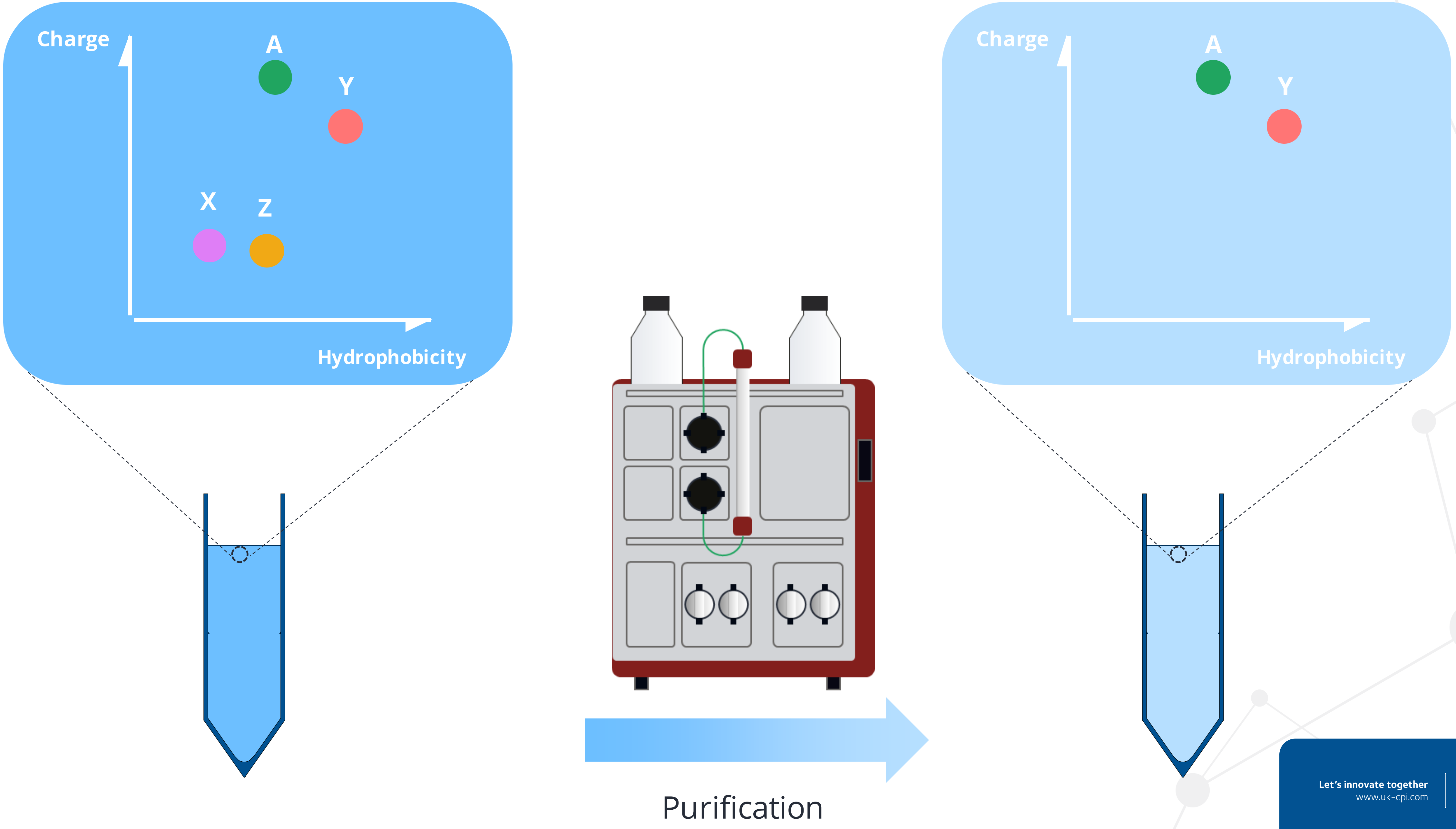
Purification Analytical Platform



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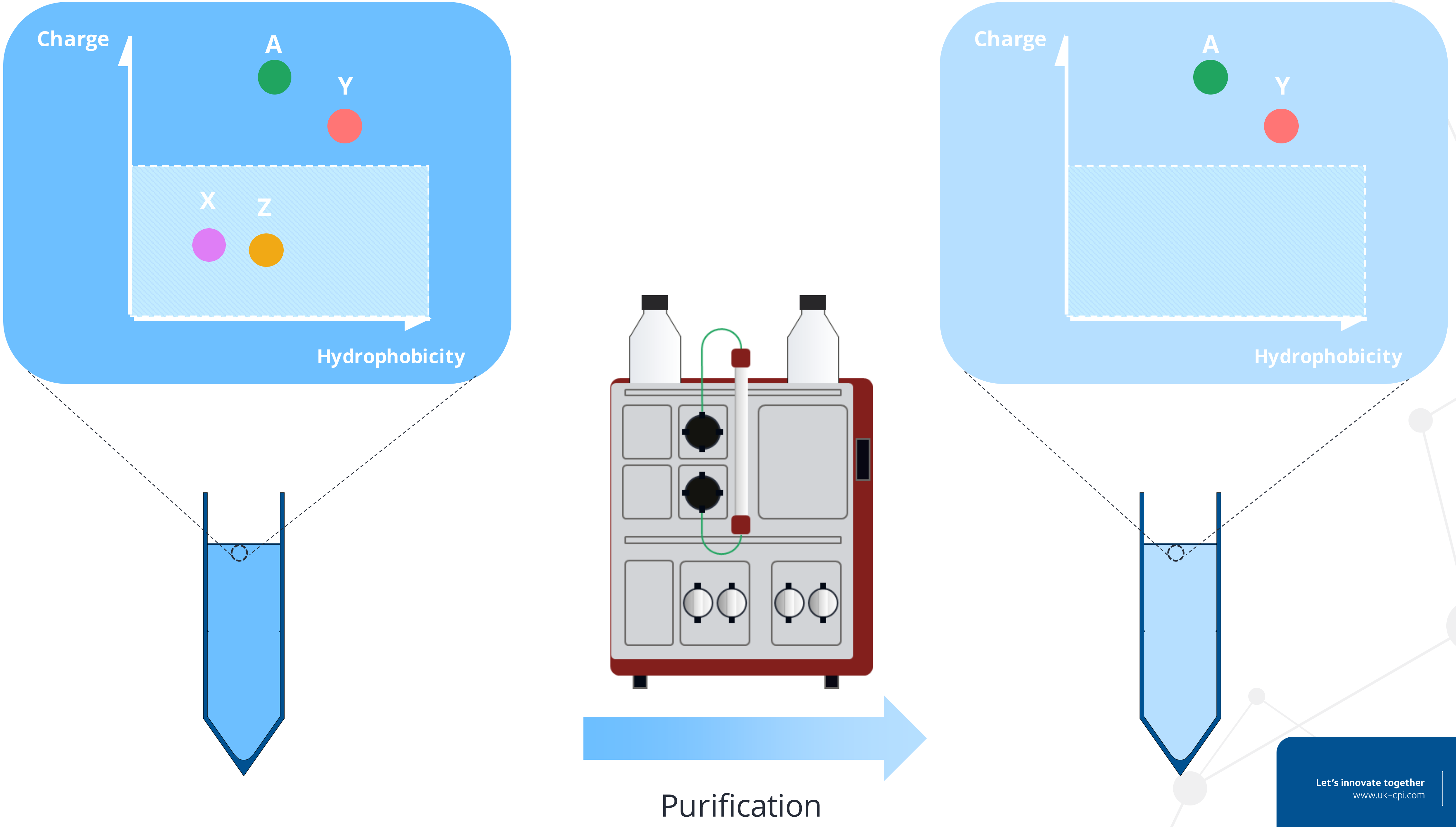
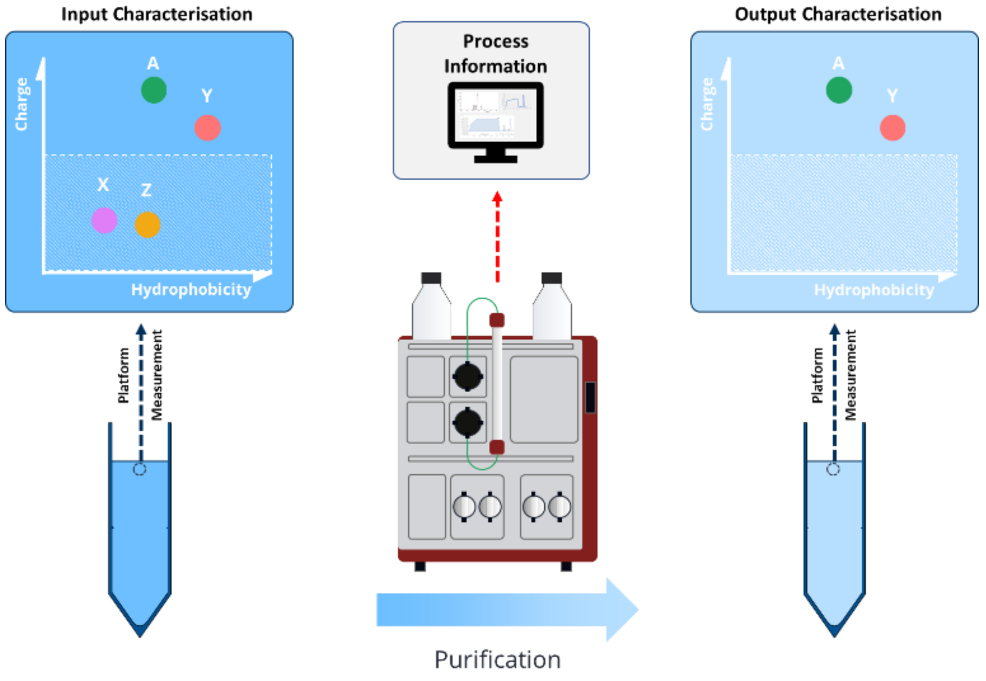


Purification Analytical Platform

Use LC/MS as a platform analytic for purification experiments.



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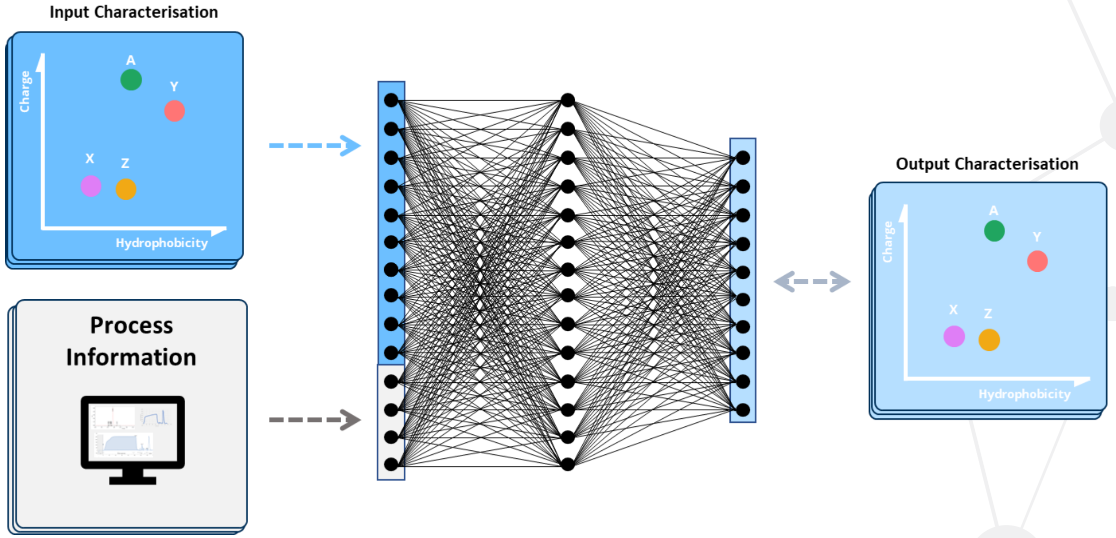
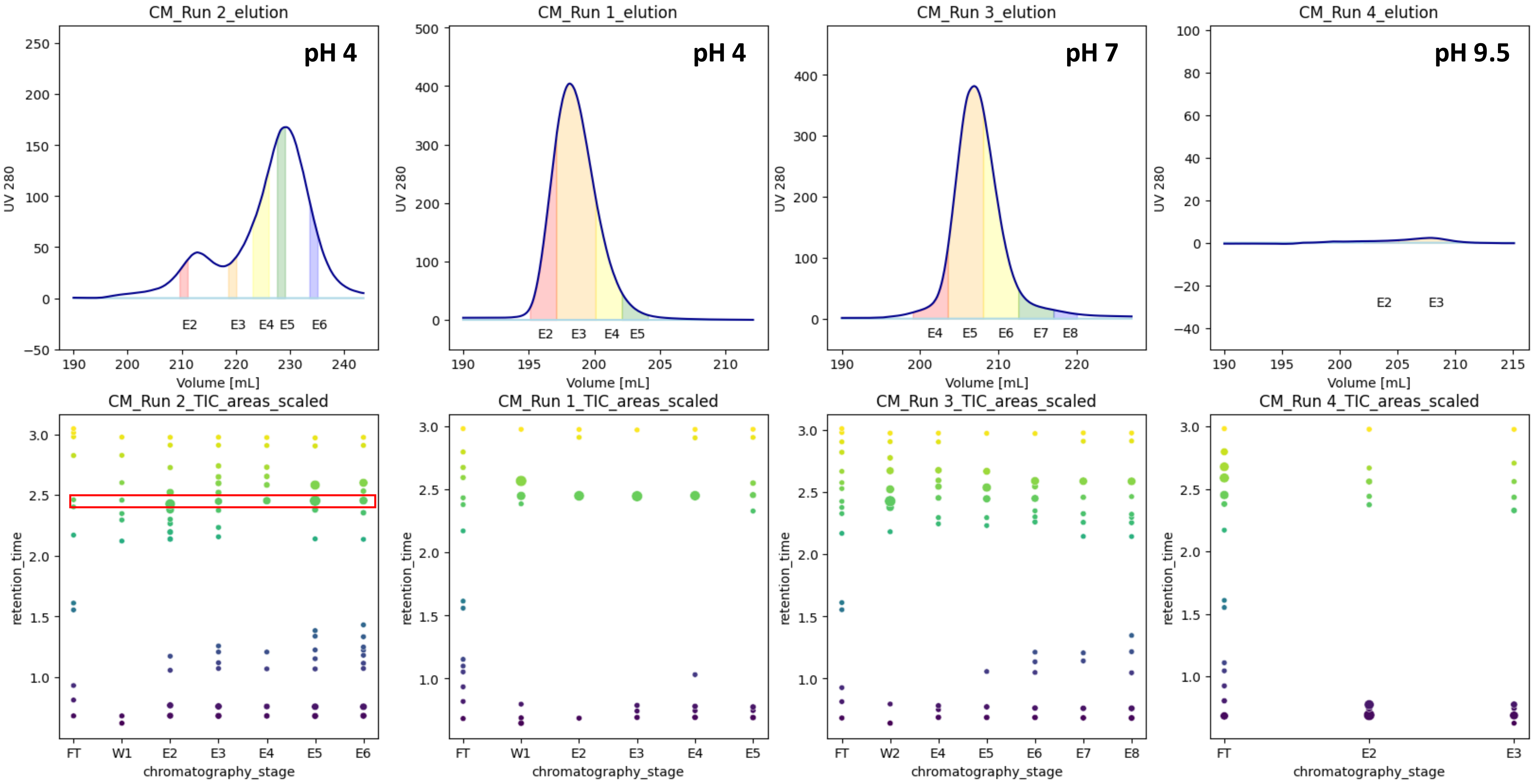


Purification Analytical Platform – Proof of Concept

Example Data – Cation Exchange Chromatography

Downstream Elutions

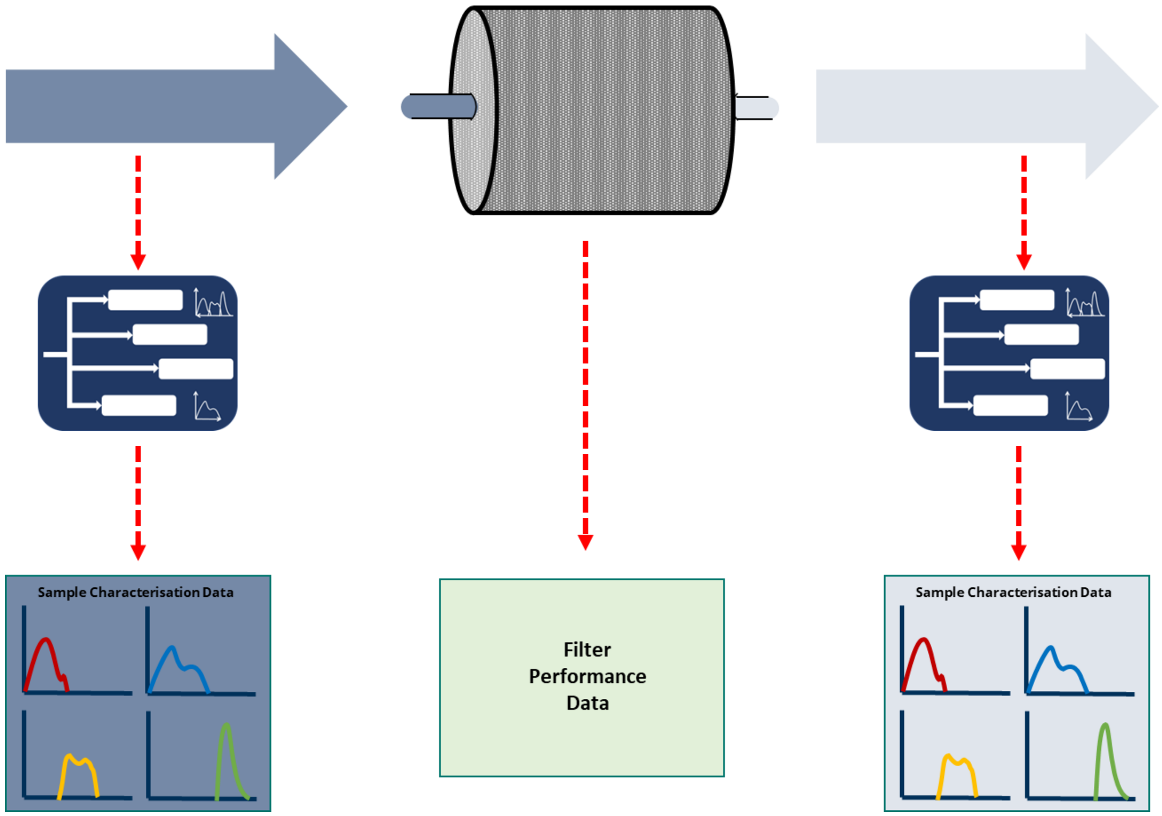
Reverse Phase LC/MS Analysis



Clarification - Objectives

Objective

Generate predictive models that can determine **filterability and filter performance** from an initial platform measurement, including predicting optimal filter trains.

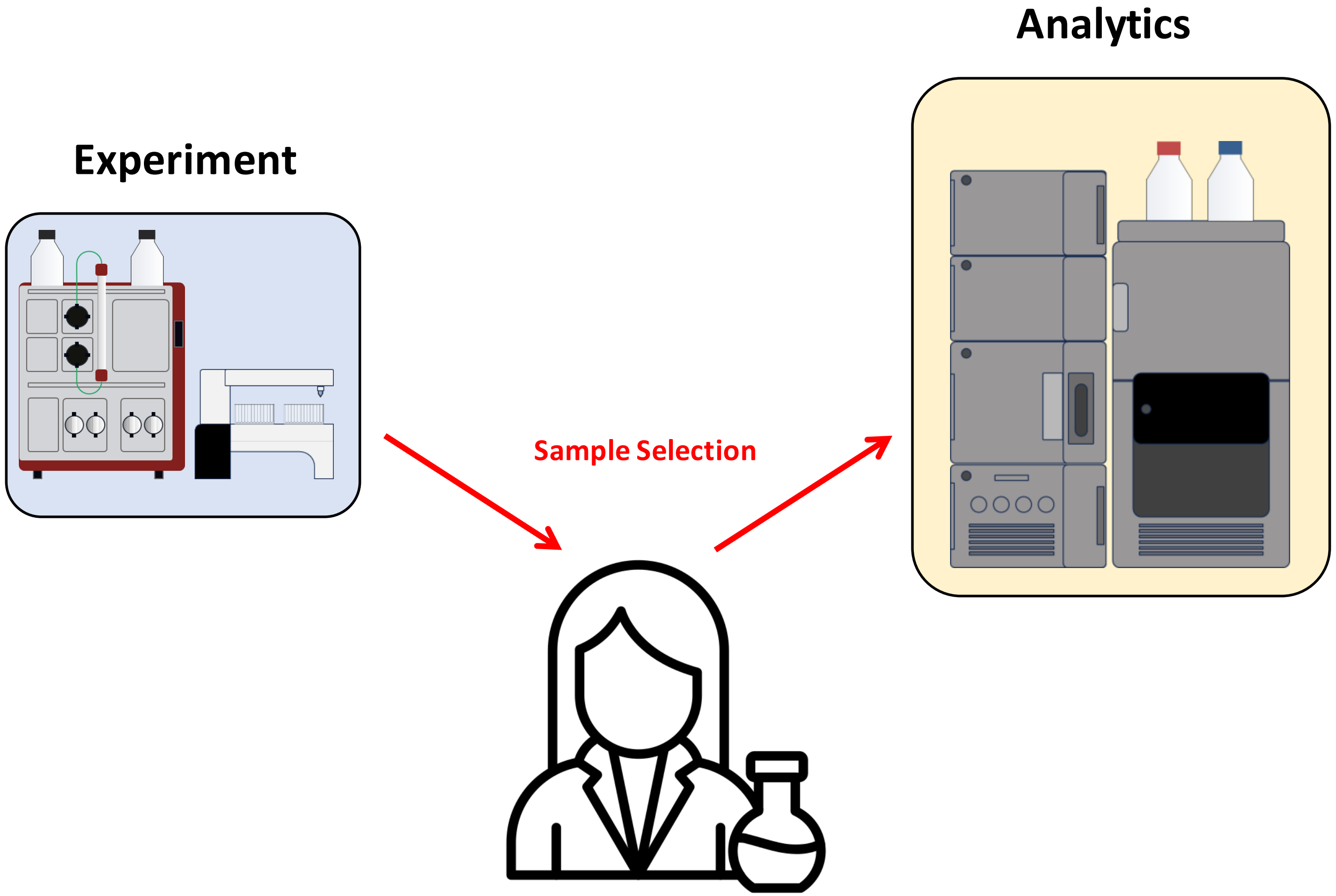


Take Samples before and after filtration

Understand how **size and charge** predict filtration behaviour and design processes accordingly.

Choose optimal filters for a given reduction in particle content and turbidity.

Automating Experiments



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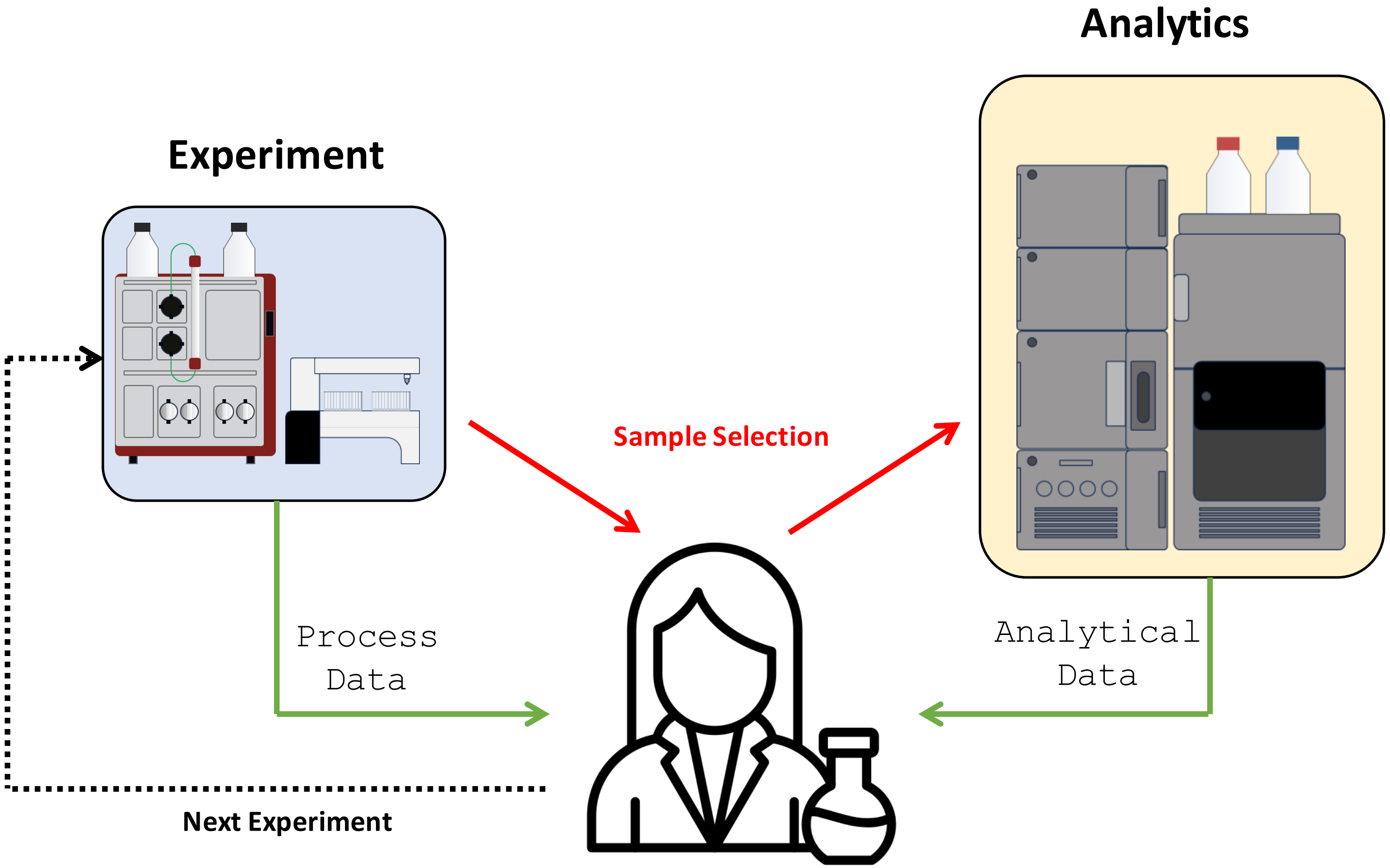

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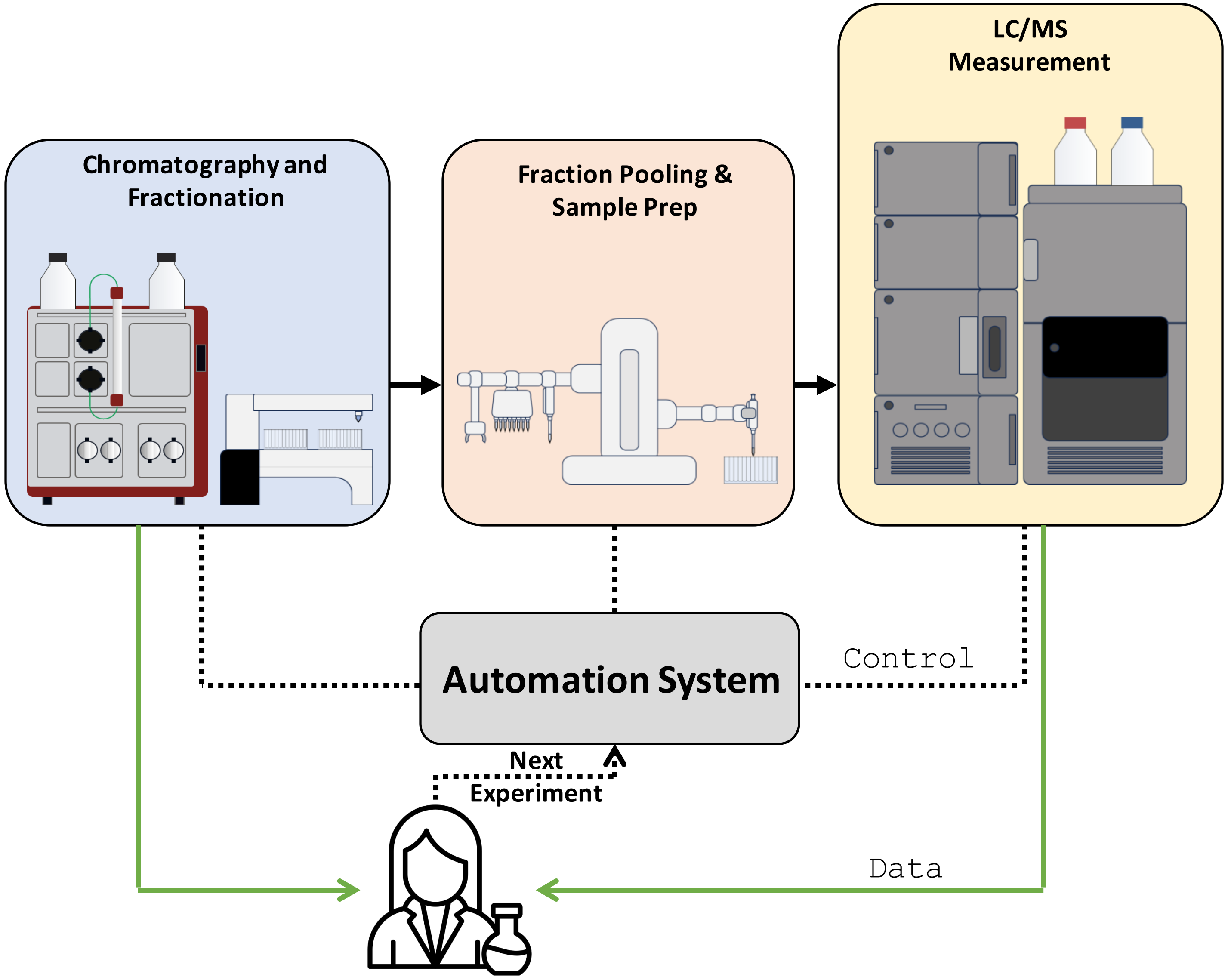
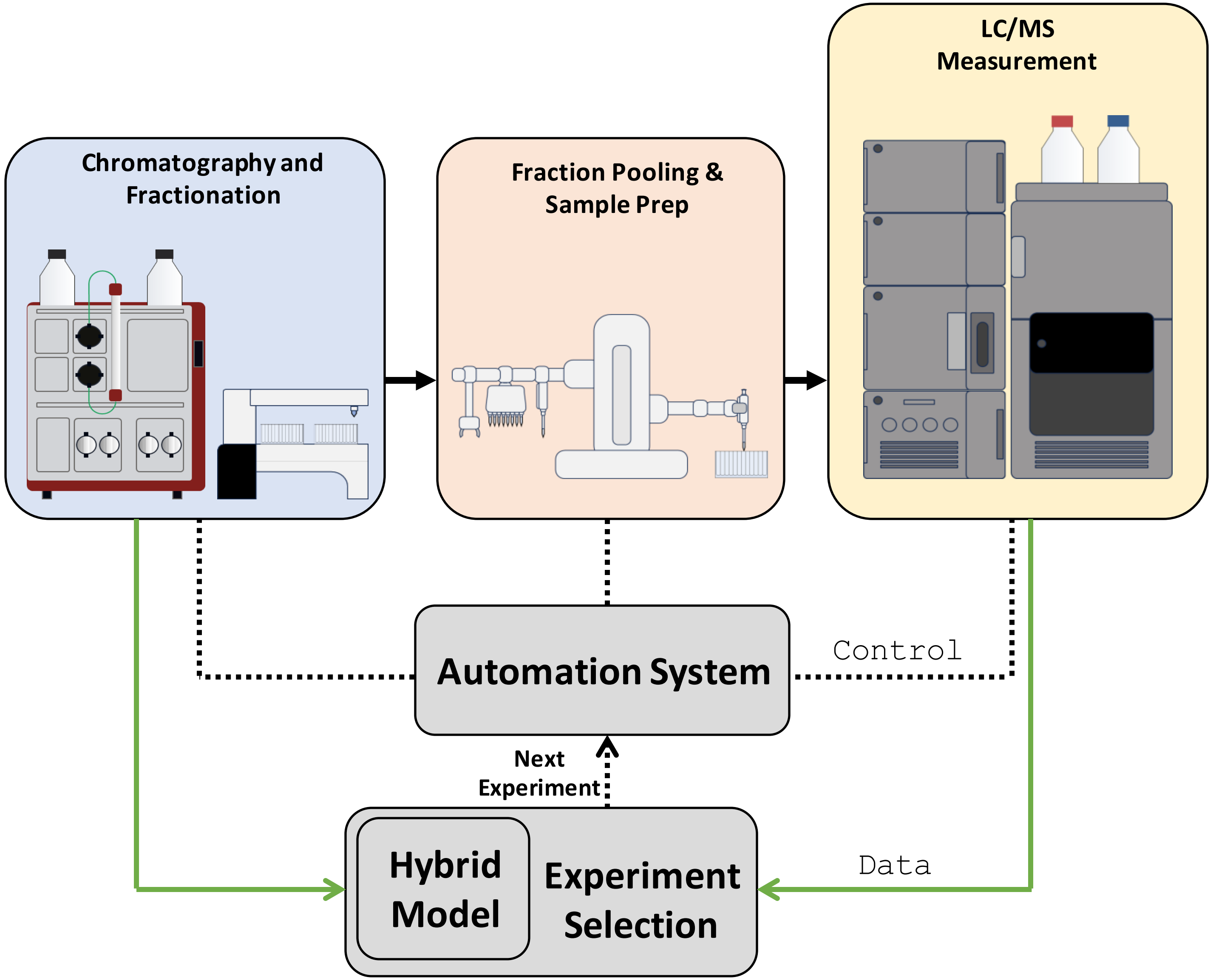


Downstream Robot Scientist



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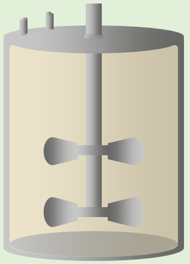
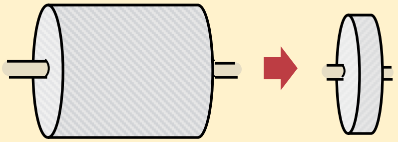
3 Key Areas

Upstream



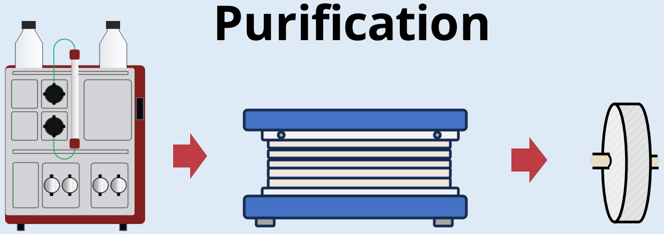
Clarification



Depth Filtration

Filtration

Purification

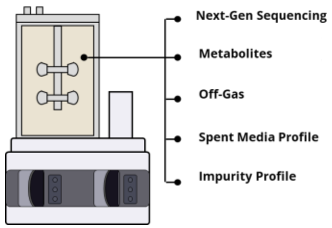


Chromatography

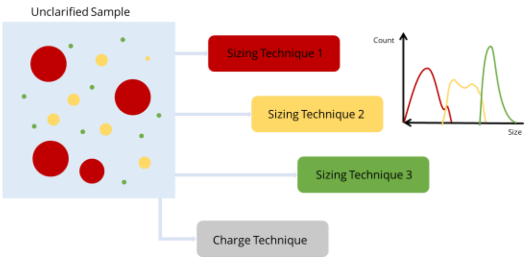
TFF

Filtration

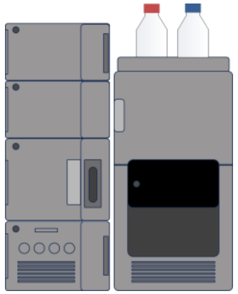
3 Analytical Platforms

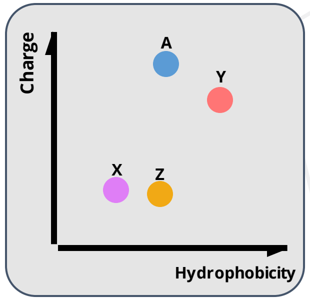


AMBR-Based
Upstream Development Platform



Size & Charge-based
Clarification Development Platform





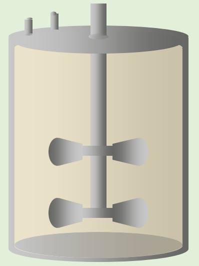
LC/MS Based
Purification Development Platform

How do we get there?

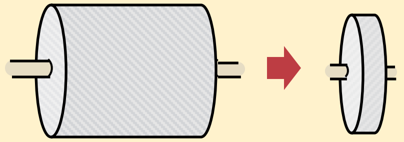
Automating Development

3 Key Areas

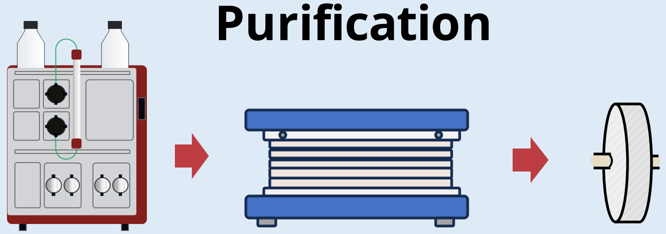
Upstream



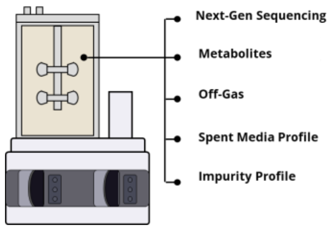
Clarification



Purification



3 Analytical Platforms

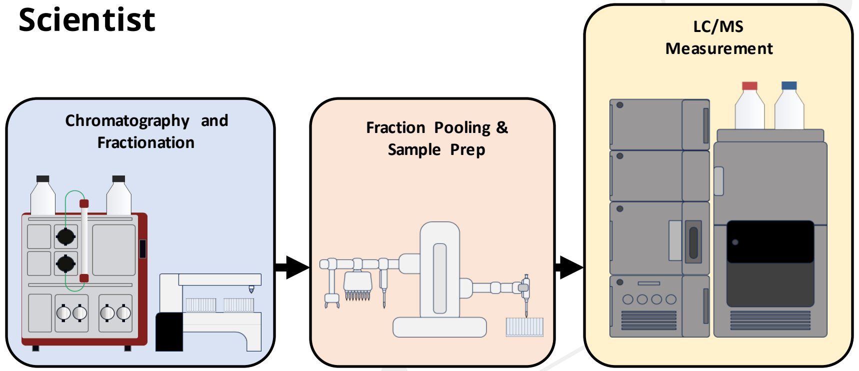


Integrating Analytics

Scoping further automation

?

Automated Downstream Scientist



DATAHOW

Hybrid Models for Chromatography

Integrate ML to Speed Up Process Development

Alessandro Butté – CEO DataHow
02 May 2024

Our Technology

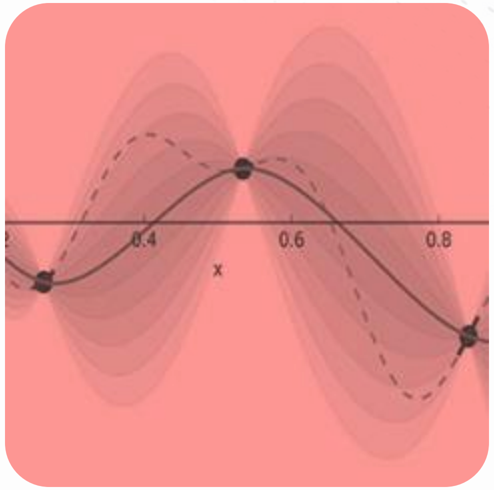
Our Technology

Hybrid Models

Allow both the reduction of data and experiments while increasing model robustness and predictivity thanks to knowledge integration.

Transfer Learning

Slash costs and risk by allowing both horizontal (from product to product) and vertical (from scale to scale) transfer of knowledge



Bayesian DoEs

Optimize experiment utility by efficiently integrating prior knowledge, risk in prediction, and process constraints

DataHow Hybrid Models the key performance driver

But what are they?

What we know about the process

Mechanistic models which describe known engineering and process knowledge

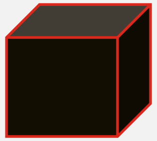
Ineffective when used alone
Unable to describe complex behaviors and relationships present in biological systems (especially in USP)

Key impact within a hybrid model:
Narrows the design space by eliminating areas which are known

Hybrid models

What we don't know

Machine learning models which determine relationships and patters from raw process data to help explain complex relationships



Of limited use for PD when used alone
High volumes of data required to produce high confidence in results (PD is data poor)

Key impact within a hybrid model:
Within a restricted area of exploration (supported by mechanistic models), the provide answers to areas of low understanding

How Hybrid Models Work

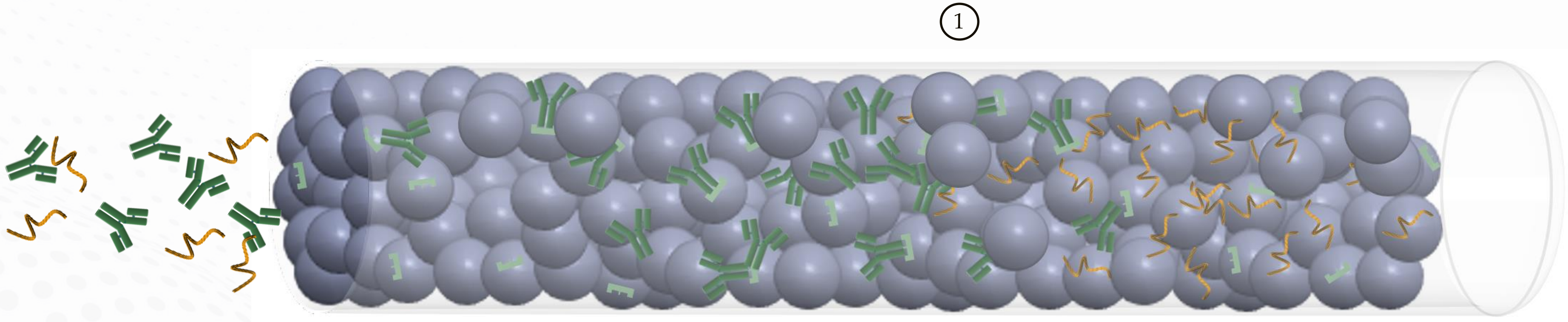
Chromatographic Modelling: State of the Art

Phenomena in the bulk/continuous phase can be well predicted with mechanistic modeling

Phenomena to consider

$$\text{①} \quad \frac{\partial c_i}{\partial t} = -v\frac{\partial (c_i)}{\partial x} + D_i \cdot \frac{\partial^2 c_i}{\partial x^2} - \phi \cdot J_i \cdot \alpha_p$$

1. Transport through the column



G. Guiochon, D. G. G. Shirazi, A. Felinger, A. M. Katti, *Fundamentals of Preparative and Nonlinear Chromatography (2nd Edition)*, Academic Press, **2006**.

D. Pfister, L. Nicoud, M. Morbidelli, *Continuous Biopharmaceutical Processes: Chromatography, Bioconjugation, and Protein Stability*, Cambridge University Press, **2018**.

Chromatographic Modelling: State of the Art

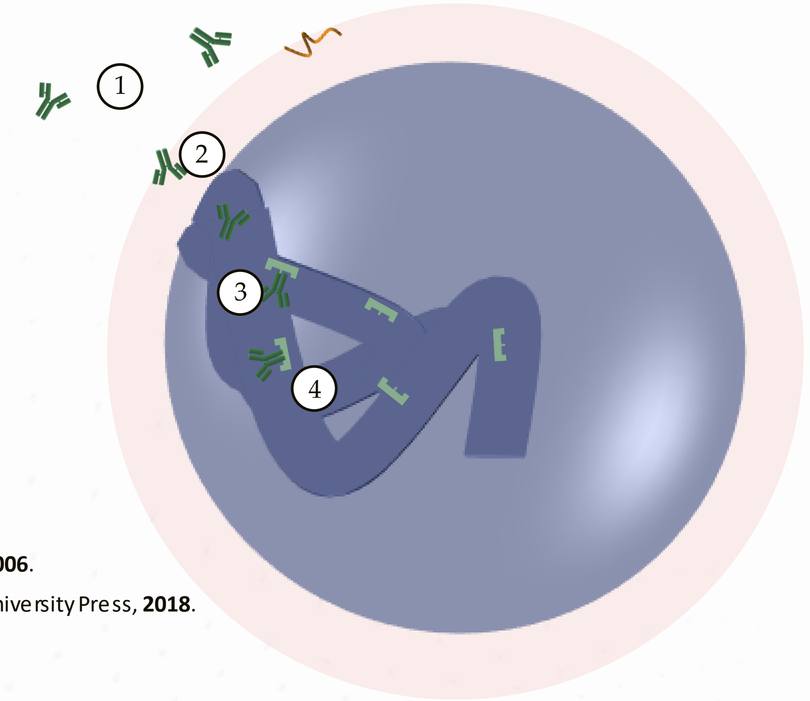
Hybrid models can be highly beneficial also for well understood processes

Phenomena in the particle phase

1. Transport through the column
2. Film transport
3. Intra-particle Transport
4. Adsorption

$$\varepsilon_p \frac{\partial c_i}{\partial t} + (1-\varepsilon_p) \cdot \frac{\partial q_i}{\partial t} = \frac{\varepsilon_p D_{p,i}}{r^2} \cdot \frac{\partial}{\partial r}\left(r^2 \cdot \frac{\partial c_i}{\partial r}\right)$$

$$\varepsilon_p D_{p,i} \left.\frac{\partial c_i}{\partial r}\right|_R = \frac{3k_f}{R} \cdot (c_{bulk,i} - c_i)$$



Kinetics in the particle phase is also very well understood but very complex to describe

G. Guiochon, D. G. G. Shirazi, A. Felinger, A. M. Katti, *Fundamentals of Preparative and Nonlinear Chromatography (2nd Edition)*, Academic Press, **2006**.

D. Pfister, L. Nicoud, M. Morbidelli, *Continuous Biopharmaceutical Processes: Chromatography, Bioconjugation, and Protein Stability*, Cambridge University Press, **2018**.

Hybrid models for Chromatography

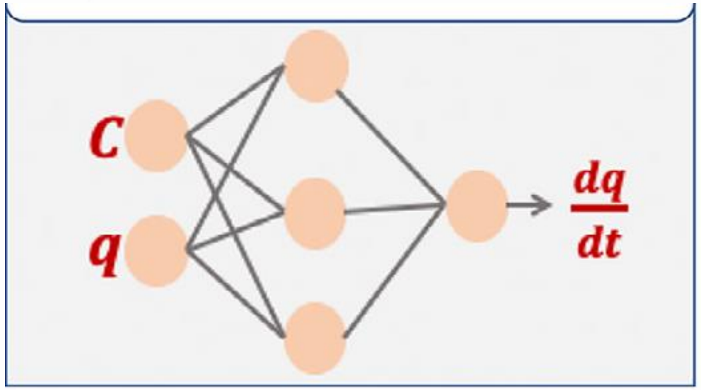
Example of model hybridization

- Lumped kinetic model as backbone
  - Scalable solution
  - Transferable to other cleaning procedures
  - Forecasting capability
- Hybridization of the uptake rate ($\frac{\partial q}{\partial t}$)
- Replace mechanistic equation with a neural network

$$\frac{\partial c}{\partial t} = \overbrace{-v\frac{\partial c}{\partial x}}^{convection} + \overbrace{D_L\frac{\partial^2 c}{\partial x^2}}^{diffusion} - \overbrace{\varphi\frac{\partial q}{\partial t}}^{mass\ transfer}$$

$$v = \frac{Q_{flow}}{A_{col}\cdot \boldsymbol{\varepsilon}} \qquad D_L = \boldsymbol{A}\frac{d_p}{2}v \qquad \varphi = \frac{(1-\boldsymbol{\varepsilon})}{\boldsymbol{\varepsilon}}$$

$$\frac{\partial q}{\partial t} = \textbf{\textit{Machine Learning}}\ (\boldsymbol{c}, \boldsymbol{q}, \dots)$$



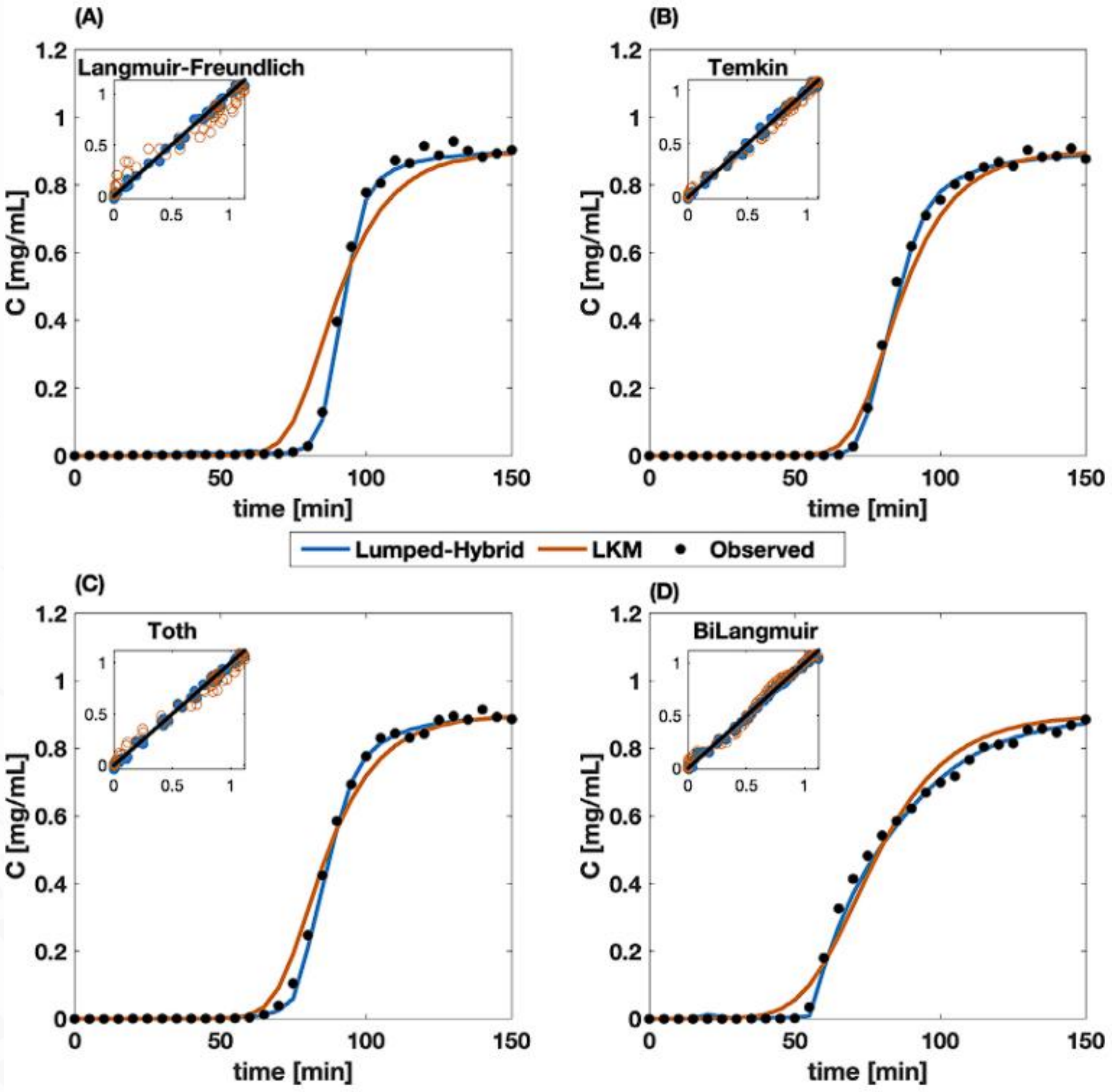
$$\frac{\partial q}{\partial t} = \boxed{NN_{mt}(q)} \cdot \boxed{(NN_{iso}(c)} - q)$$

Pore Mass Transport

Equilibrium Isotherm

- Narayanan H. et al., Ind. Eng. Chem. Res. (2022)
- Narayanan H. et al., Biotechnol. Bioeng. (2019)

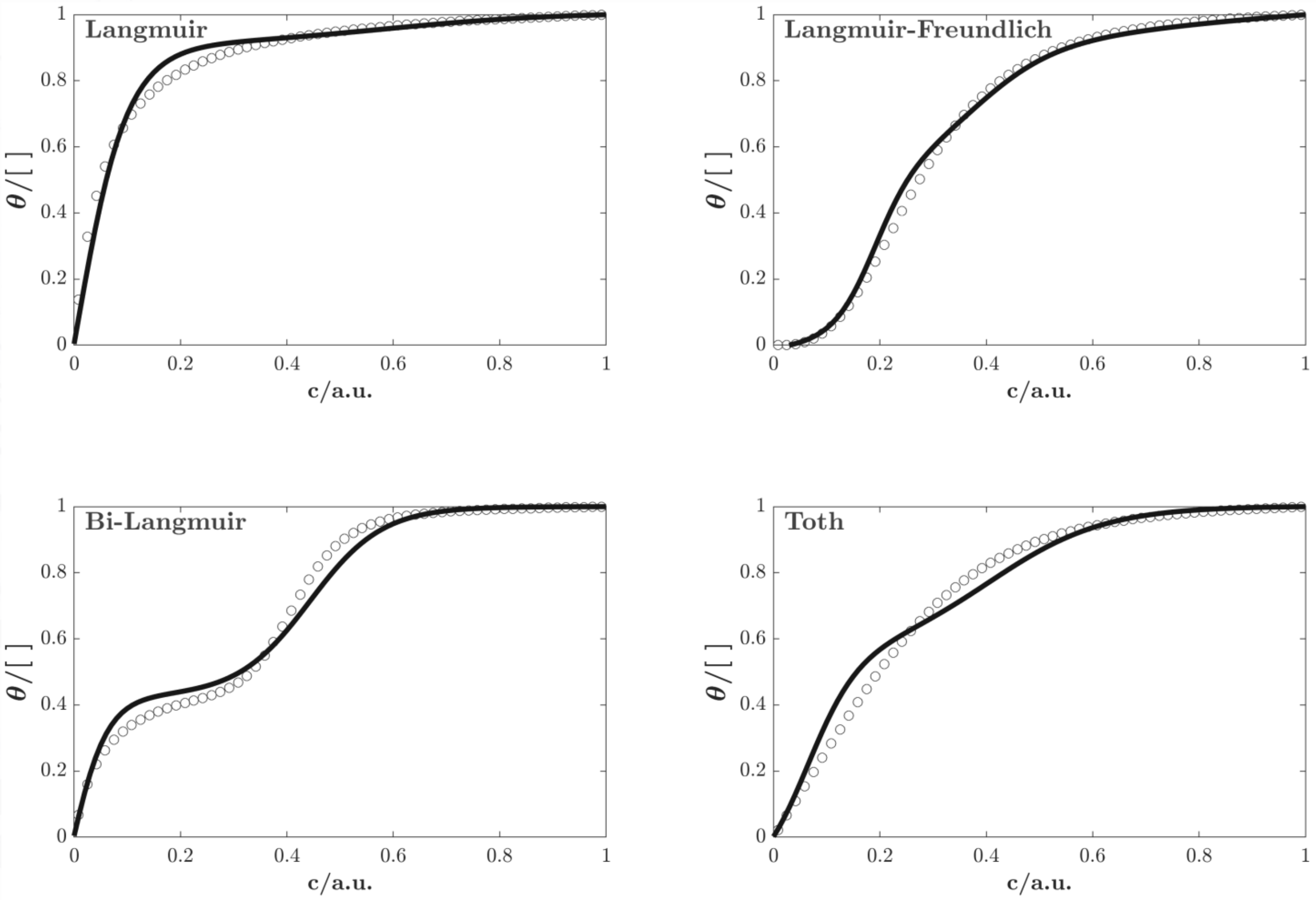
Different Adsorption Isotherms



Narayanan H. et al., 2021 J. Chrom. A

Hybrid Models: Insights

Using hybrid models for mechanistic understanding of the process



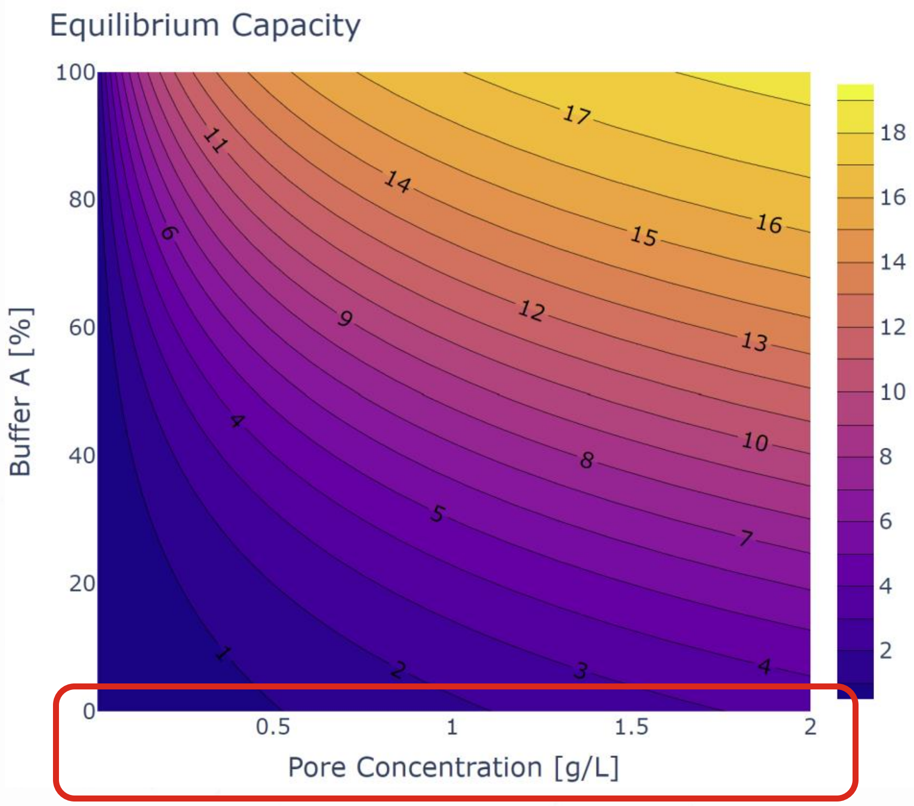
$$J = \boxed{ANN_{mt}(q)} \cdot \boxed{(ANN_I(c)} - q)$$

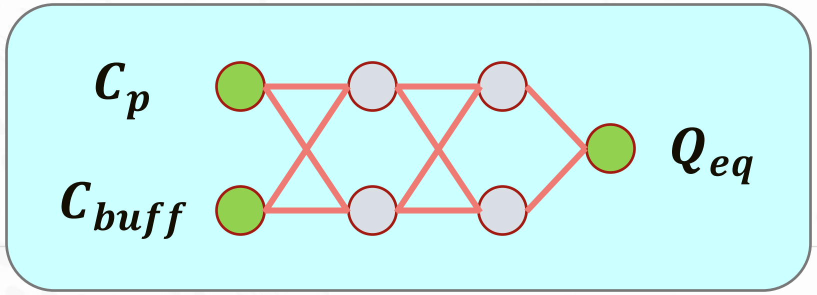
Mass Transport

Equilibrium Isotherm

In-Silico Isotherm	R^2 Assumed Isotherm LM	LF	BL	TH	TM
LM	**0.97**	0.23	0.25	0.51	0.46
LF	-1.46	**0.99**	0.85	0.88	0.52
BL	-0.56	0.85	**0.98**	0.86	0.80
TH	0.11	0.85	0.89	**0.97**	0.94
TM	-0.28	0.89	0.92	**0.95**	0.93

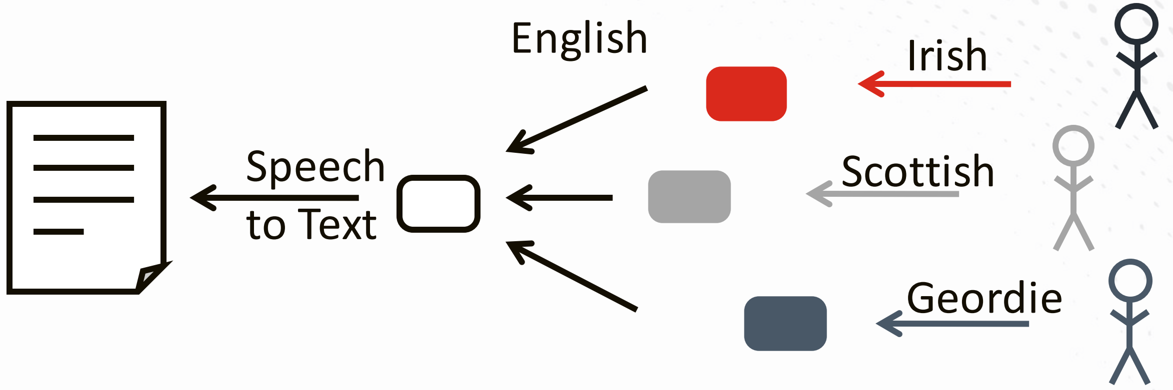
Physical Consistency of NNs

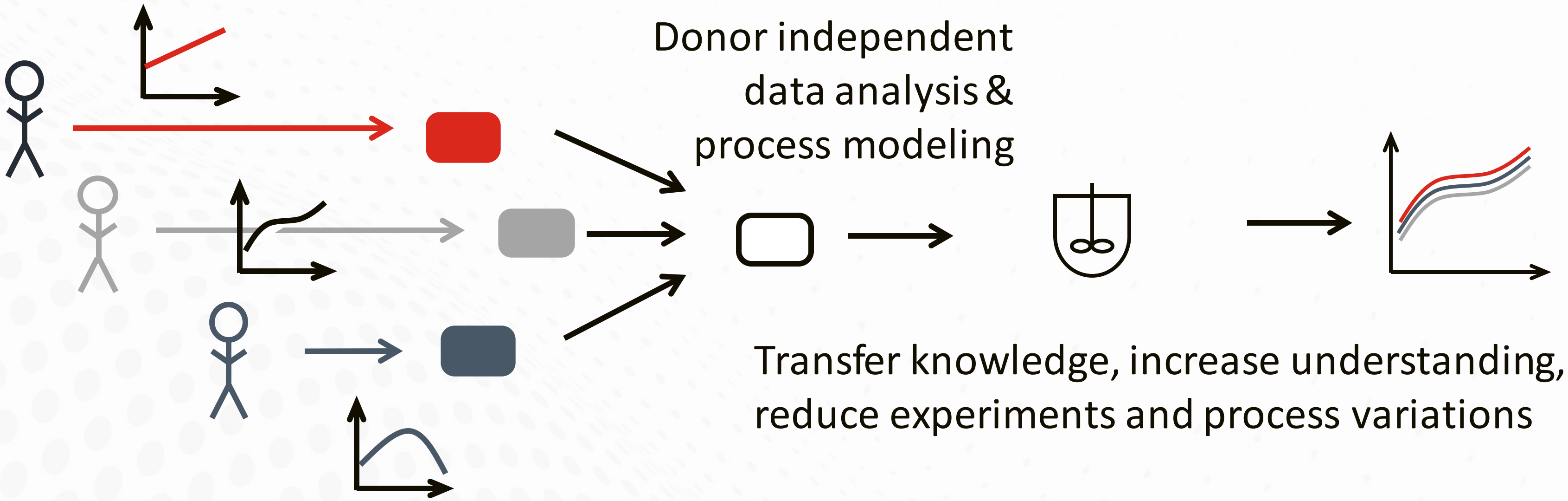




DataHow's proprietary knowledge transfer technology allows to bridge between donors & reduce experimental effort for validation.

Inspired by speech recognition, DataHow has developed a proprietary knowledge transfer technology that can be used to compare data of the same unit operation for various scales/sites.





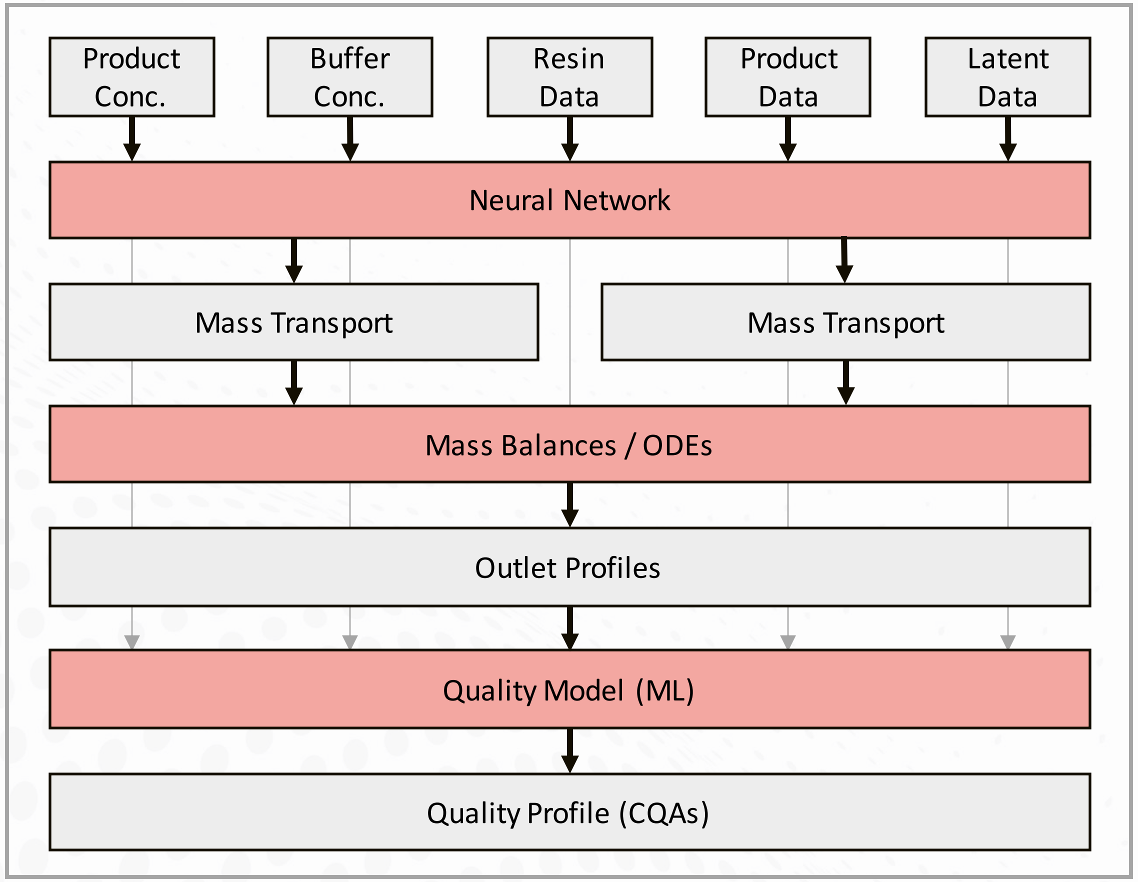
Transfer knowledge, increase understanding, reduce experiments and process variations

Overall Procedure

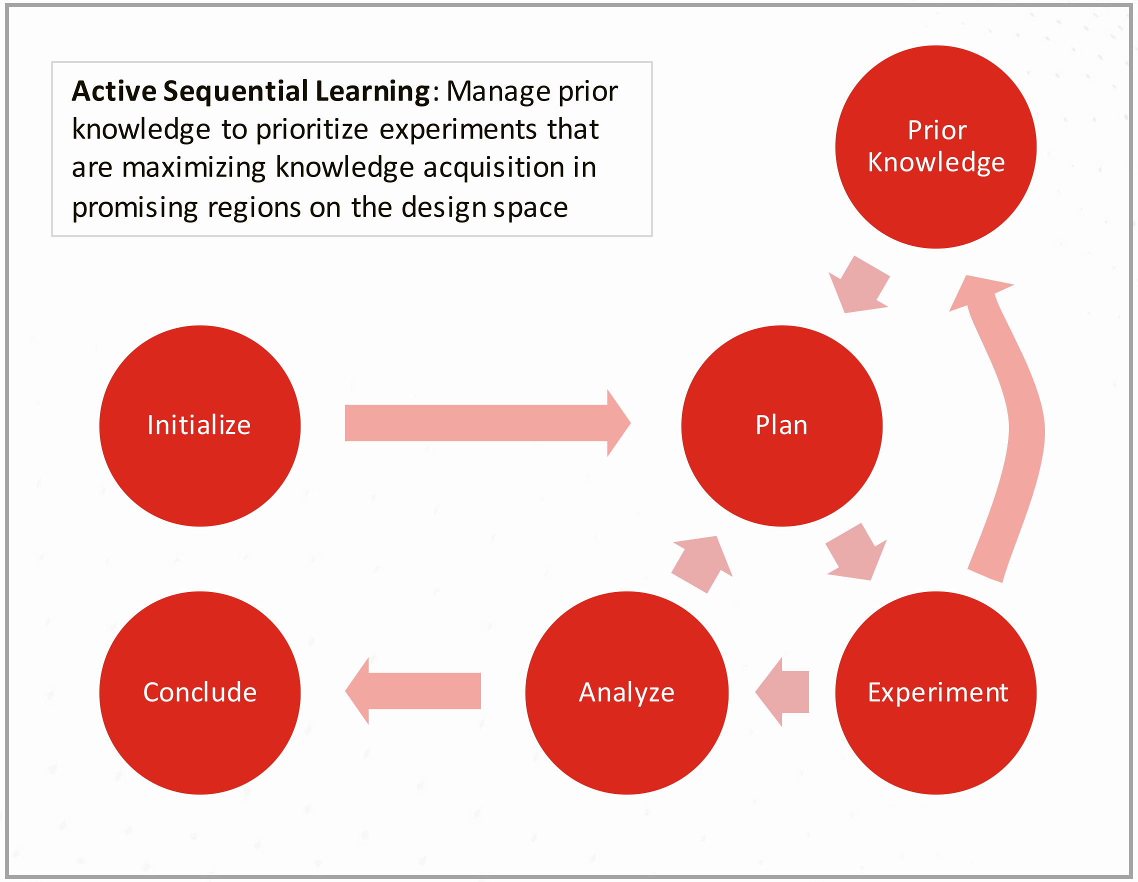
Product Informed Hybrid Model

Towards the definition of an active sequential learning procedure

Model Structure



Learning and Design Procedure



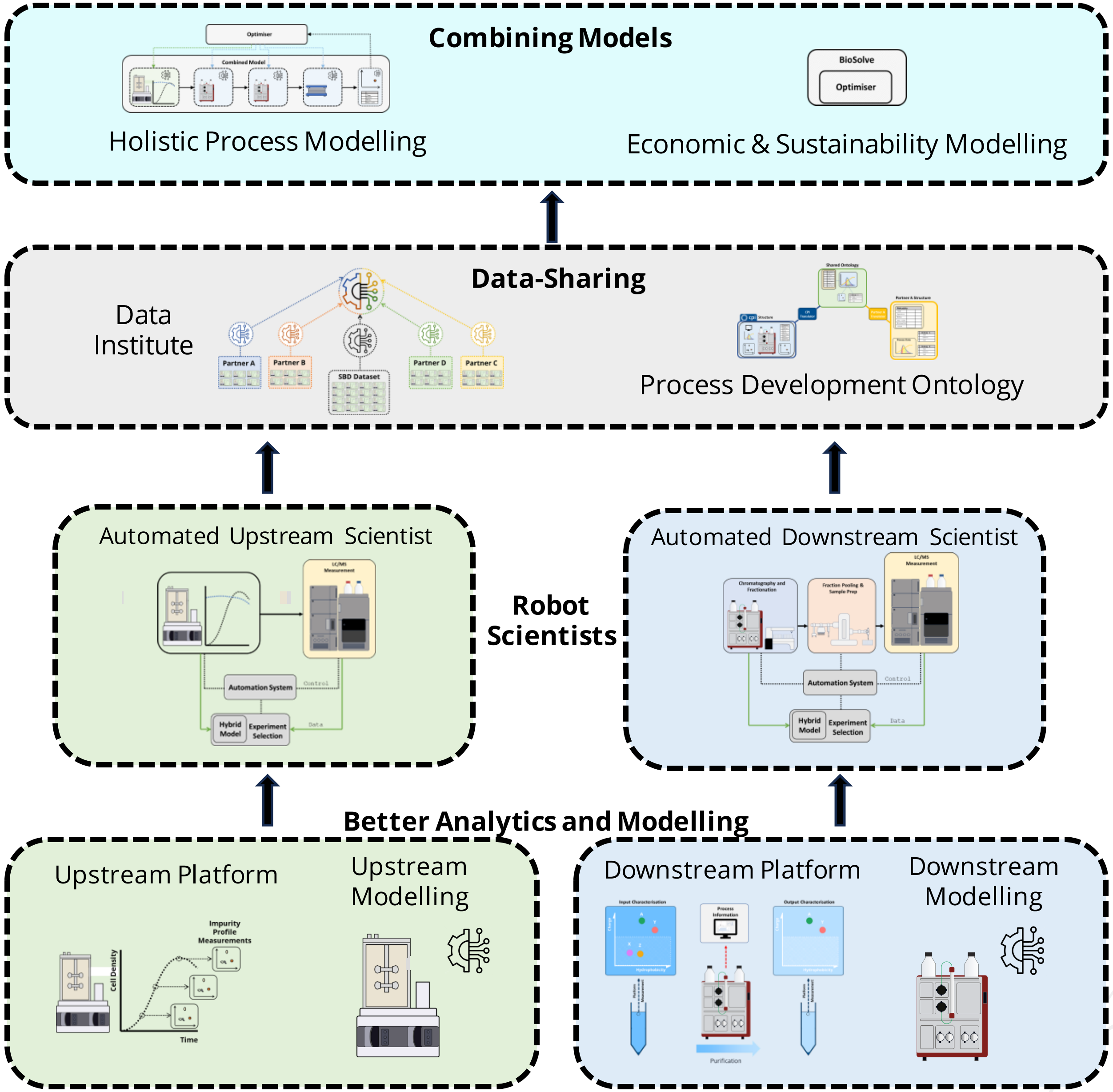
Smart Bioprocessing Grand Challenge

Join us in transforming the future of bioprocessing!

Full Grand Challenge Structure

Rethinking Datasets

Better Development Tools



Questions