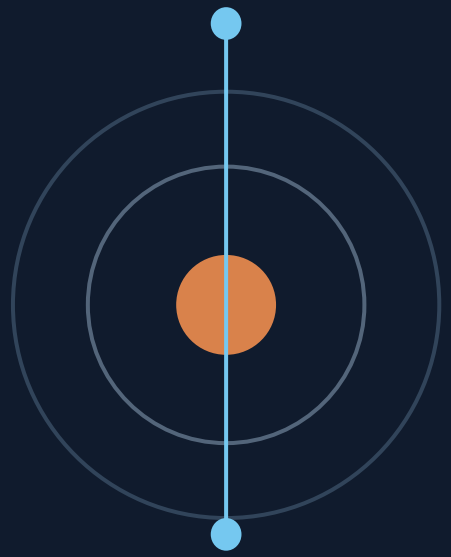
Downstream 2.0:

The PAT-Driven, Data-Enabled Future of Bioprocessing

From flow-through purification to intelligent, model-based DSP



Andrew Falconbridge | Try3i

About Me and Try3i

Turning bioprocess technology into executable strategy.

TRY3I =

INTENSIFICATION

INNOVATION

IMPROVEMENT

Making bioprocessing smaller/faster, adopting what matters, and embedding it sustainably.

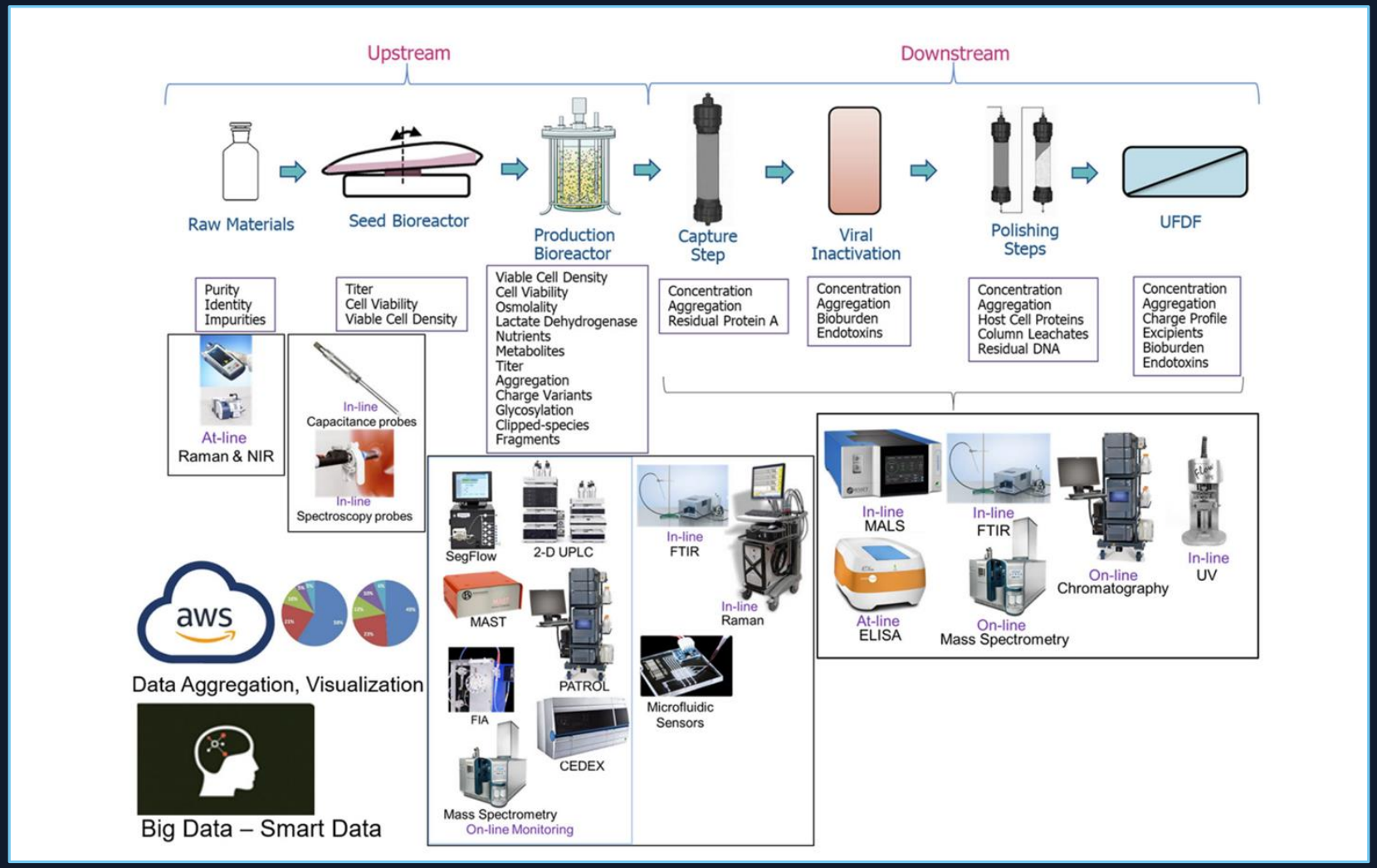
EXPERIENCE

- Led PAT, modelling, digital, and USP/DSP intensification teams
- Ran development and GMP manufacturing organizations
- Advised on process and digital strategy across the bioprocess lifecycle

RELEVANCE TO THIS TALK

- PAT is the focus today, but I position it as one enabler in a broader intensification and control story
- My work is about turning technology into executable strategy, not just pilots

PAT as an enabler



Advantages of Process Analytical Technology (PAT)



Fast acquisition time



Real time analytics



Better process understanding



Process control



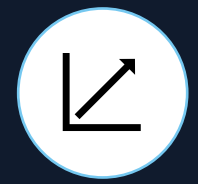
Reduced waste



Reduced cost

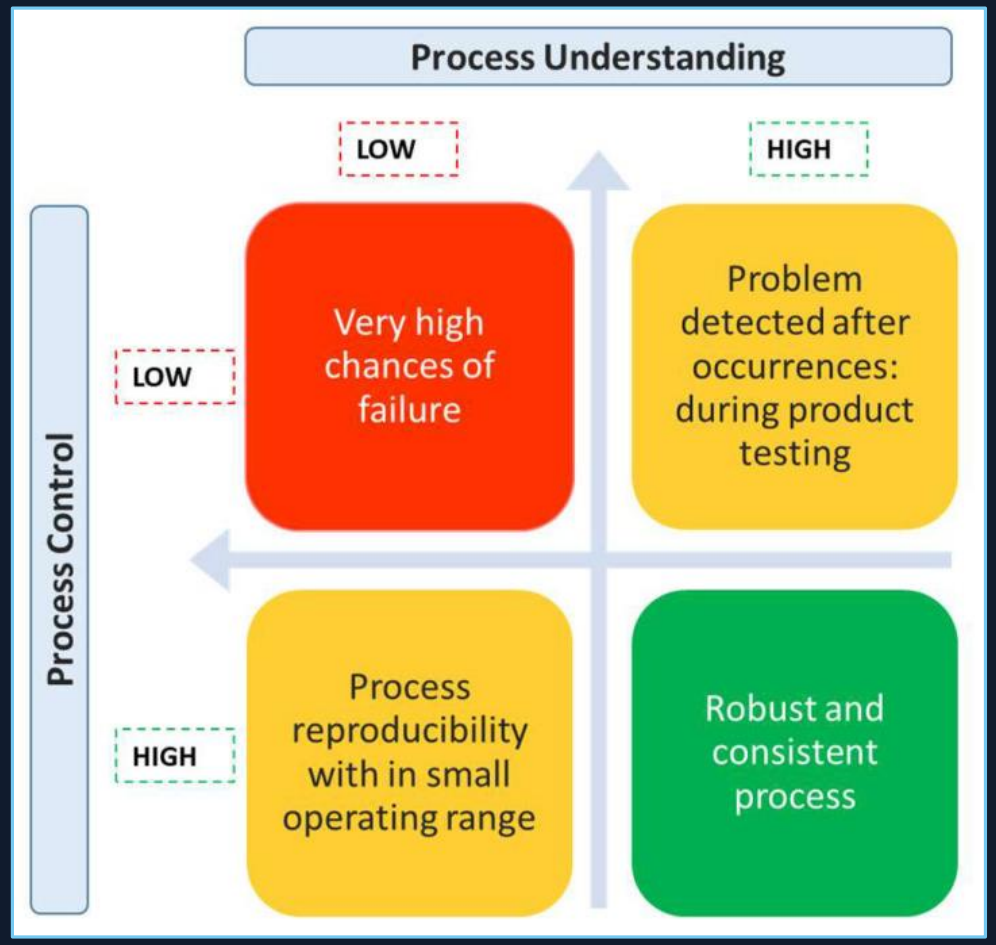


Reduced analytical burden



Increased process yields

Process Understanding



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Every platform leap begins with an enabling technology

Technology compounds through a repeatable progression.

1 → **NEW TECHNOLOGY**

2 → **NEW DATA**

3 → **NEW UNDERSTANDING**

4 → **NEW CONTROL**

5 **NEW OPERATING MODEL**

rDNA + cell-line engineering → modern biologics

High-cell-density culture + perfusion → intensified upstream

Single-use technology → flexible, multi-product facilities

Advanced chromatography + filtration → intensified / continuous DSP

QbD + platform science → systematic, risk-based development

THE QUESTION

What enabling layer is still missing from downstream?

The next leap is Data and intelligent control—not hardware alone

01

PAT

SEE

Inline + at-line sensing

02

DIGITAL

CONNECT

Integrated data backbone

03

AUTOMATION

ACT

Model-based decisions

NO DATA → NO MODELS → NO REAL-TIME CONTROL

Upstream already runs on continuous evidence

Dense live data supports models, digital twins, and real-time adjustment.

CELL STATE

Turbidity, capacitance, dielectric spectroscopy

METABOLITES

Glucose, lactate, glutamine, ammonium via Raman / NIR

PRODUCT

Titer, osmolality, selected CQAs via spectroscopy + models

PROCESS UNDERSTANDING

Continuous data streams feed models and digital twins.

ADVANCED CONTROL

Feed, bleed, and perfusion rate adjust in real time.

USP has the data density to model and control.

DSP has historically lacked it.

Many upstream signals. Limited downstream live data.

The asymmetry drives different decision models.

BIOREACTOR / USP

- Cell density, viability, pH, DO
- Glucose, lactate, glutamine, ammonium
- Titer, osmolality, selected CQAs
- Live trends used for control decisions

DOWNSTREAM / DSP

- pH
- Conductivity
- UV 280 nm
- Offline: purity, aggregates, impurities, HCP, DNA

CONSEQUENCE

USP continuous measurements → understanding → control

DSP limited live signals + delayed results → static decisions

The process moves in minutes. The answer arrives later.

DSP events unfold faster than conventional analytics can respond.

CRITICAL DSP EVENTS

01 **CHROMATOGRAPHY BREAKTHROUGH**
Seconds to minutes

02 **PEAK / IMPURITY-FRONT SHIFTS**
Seconds to minutes

03 **MEMBRANE FOULING / FLUX DECLINE**
Minutes

TYPICAL OFFLINE RESULT

HOURS TO DAYS

By the time the answer arrives, the critical decision window has already closed.

Static decisions are applied to dynamic, flow-through processes.

Real-time PAT lets DSP see—and act—as the process evolves.

The historical barrier was measurement feasibility

Interest was never the constraint; practical, timely measurement was.

01 **FAST, FLOW-THROUGH OPERATIONS**
Decisions are required in seconds—not hours.

02 **COMPLEX ANALYTICAL TARGETS**
Product, aggregates, fragments, and impurities shift with the matrix.

03 **SINGLE-USE INTEGRATION**
Legacy sensors were designed for stainless systems.

04 **SAMPLING + SENSOR PLACEMENT**
DSP has no universal probe set equivalent to a bioreactor.

05 **LIMITED HISTORICAL BUSINESS CASE**
Offline testing was considered adequate; urgency was lower.

THE REAL BARRIER

PRACTICAL MEASUREMENT (Inline/At line)

timely
single-use compatible
decision-ready

The barrier was feasibility—not a lack of interest in better control.

Three advances have made PAT executable in DSP

What was once aspirational can now be engineered into the process.

01	**SENSOR-READY SINGLE-USE**	Single-use–compatible sensors and integrated flow cells make PAT feasible on modern DSP skids.
02	**AUTOMATED AT-LINE SAMPLING**	Reproducible sampling into at-line analyzers closes gaps where inline CQA measurement remains difficult.
03	**DEVELOPMENT SPEED**	Inline and at-line data enable decisions in hours—not days—and accelerate scale-up and tech transfer.

THE KILLER USE CASE

HOURS

not days

FEWER RUNS
FASTER ITERATION
LOWER DEVELOPMENT COST

PHYSICAL ACCESS + AUTOMATED SAMPLING + RAPID LEARNING = EXECUTABLE PAT

The first payback is faster learning

The business case starts long before real-time release.

TRADITIONAL DSP DEVELOPMENT

Run the experiment ↓

Collect samples ↓

Wait for offline results ↓

Interpret the data ↓

Redesign the next experiment

More runs • longer timelines • higher cost

PAT-ENABLED DEVELOPMENT

Run the experiment ↓

See behavior in real time ↓

Adjust or terminate intelligently ↓

Link signals to CQAs ↓

Build stronger models + controls

Faster learning • fewer blind runs • stronger insight

The first business case is faster, better process development.

Guardian advertisement in snapshots

01



02



03



04



Development PAT reveals what offline snapshots miss

Live evidence connects process behavior to yield and product quality.

PAT CAN REVEAL

- Product concentration changes across the train
- Breakthrough onset and progression
- Peak shape and impurity-front response to loading
- Membrane fouling and flux decline
- True UF/DF endpoint attainment buffer and excipient behaviour
- How conditions influence yield and quality
- Signals predictive of critical quality attributes

FROM **“Run, sample, wait, interpret”**

TO **“Observe, understand, model, optimize”**

From development evidence to manufacturing control

Learn broadly; deploy selectively.

1 DEVELOPMENT	2 PROCESS UNDERSTANDING	3 CONTROL STRATEGY	4 MANUFACTURING	5 REAL-TIME RELEASE
• Explore with a broad PAT toolkit	• Define ranges + decision rules	• Choose robust, relevant, fast measures	• Monitor, control, and handle exceptions	• Use validated models + data
• Link signals to CQAs / CPPs	• Build robust outcome models	• Decide what belongs in manufacturing	• Use endpoints and feedback	• Support release where justified

Development is where we learn what matters.

Manufacturing is where we deploy what has been proven to matter.

Deploy what has been proven to matter

Use the smallest measurement set that can change the right decisions.

CHROMATOGRAPHY

- Real-time pooling + cut-point decisions
- Load optimization from breakthrough monitoring

UF / DF

- Endpoint control from concentration or buffer composition
- Fouling detection from flux + pressure trends

VIRAL INACTIVATION / HOLDS

- Automated verification of pH, temperature, and time

POLISHING / FORMULATION

- Aggregate or particle monitoring for final-state confirmation

BENEFITS **tighter control • lower variability • higher yield + consistency • faster deviation response**

Real-time release is an outcome—not the starting point

Credibility is earned through a sequenced evidence chain.



PAT begins in development, where it accelerates learning.

Learning defines the control strategy; the strategy enables deployment.

Only then does real-time release become a credible endpoint.

DEVELOPMENT → EVIDENCE → CONTROL → RELEASE

PAT accelerates development—and unlocks smarter manufacturing

01 DEVELOPMENT

LEARN FASTER

More understanding from every run

- **Understanding** See process dynamics—not just endpoints
- **Decisions** Act faster with dense, real-time evidence
- **Models** Use more data points with fewer experiments
- **Acceleration** Shorten development and reduce QC burden

02 MANUFACTURING

RUN SMARTER

Control what truly drives performance

- **Right control** Act on the variables that matter
- **Flow** Remove blocking IPCs and capacity-consuming waits
- **Automation** Build trust in model-based process decisions
- **Release** Create the foundation for real-time release

UNDERSTANDING → MODELS → CONTROL → AUTOMATION → REAL-TIME RELEASE

PAT matters when it changes a decision
Problem before technology

Instrumentation without linkage, governance, and action creates data—not value.

THREE FAILURE MODES

01 **SENSOR WITHOUT LINKAGE**
No explicit CQA / CPP decision tied to the measurement.

02 **MODEL WITHOUT GOVERNANCE**
No validation or lifecycle plan.

03 **DATA WITHOUT ACTION**
Collected and stored—but never used to drive a decision.

STRATEGIC PAT

- Start from business and product goals
- Map CQAs / CPPs → PAT tools → data architecture → control + release
- Integrate QA/QC and regulatory strategy from day one

The goal is not maximum instrumentation. It is sufficient information to make better decisions.

Faster development. Smarter manufacturing. Safer scale-up.

01

DEVELOPMENT

FEWER

runs to understand design space

- Richer datasets for models
- Shorter timelines
- Lower resource use

02

MANUFACTURING

LIVE

visibility into process state

- Tighter control
- Lower batch variability
- Path to real-time release

03

STRATEGIC

READY

for continuous / intensified DSP

- Flexible platforms
- More robust operations
- Reduced QC burden

Turn DSP 2.0 ambition into an executable roadmap

01	**DEFINE**	PAT + digital strategy aligned to pipeline and capacity
02	**PRIORITIZE**	Real-time pooling • UF-DF endpoints • continuous chromatography
03	**DESIGN**	Technology • architecture • integration • model governance
04	**ENABLE**	Control strategy • RTRT justification • CMC narratives

ONE-DAY STRATEGY WORKSHOP | **FOCUSED UNIT-OP PILOT** | **MULTI-SITE PROGRAM DESIGN**

Vendor-neutral. Product-led. Built for implementation.

The Evolution to Smarter Manufacturing

FROM BATCH TESTING → TO QbD → TO PROCESS CONTROL

MORE DATA / BETTER UNDERSTANDING
STRONGER CONTROL / FASTER PROGRESS

1. Traditional Batch Testing

QUALITY IS ONLY KNOWN AFTER THE EVENT

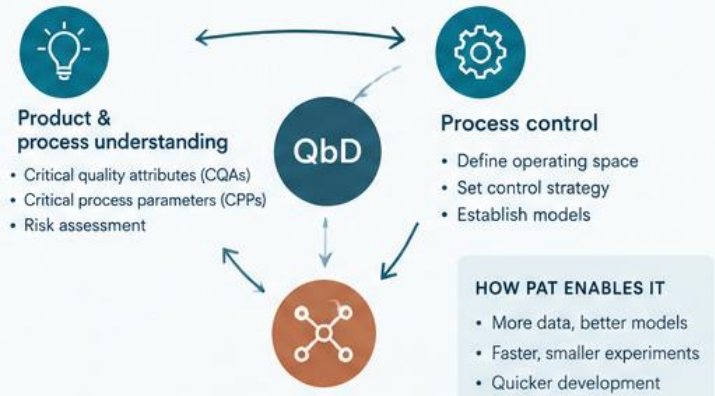


THE PROBLEM

- No real-time visibility
- Quality only known after testing
- Risk of batch failures, rework and delays
- Limited process understanding

2. Quality by Design (QbD)

BUILT ON PRODUCT & PROCESS UNDERSTANDING AND PROCESS CONTROL



Product & process understanding

- Critical quality attributes (CQAs)
- Critical process parameters (CPPs)
- Risk assessment

Process control

- Define operating space
- Set control strategy
- Establish models

PAT in development

- In-depth process understanding
- High-frequency data
- Supports modelling and design of control strategy

HOW PAT ENABLES IT

- More data, better models
- Faster, smaller experiments
- Quicker development timelines

3. Process Control

WHAT WAS LEARNED IN DEVELOPMENT IS NOW MONITORED AND CONTROLLED



FDA defines PAT as

'a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing)'

THE RESULT

- Real-time visibility and control
- Reduced variability
- Higher yields and productivity
- Pathway to real-time release

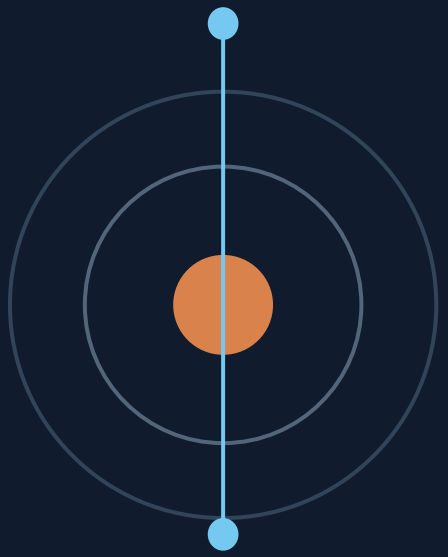
PAT IS THE BRIDGE

BETWEEN UNDERSTANDING AND CONTROL

MORE DATA → BETTER MODELS → SMARTER DECISIONS → A MORE ROBUST, EFFICIENT AND FLEXIBLE MANUFACTURING FUTURE

DSP 2.0 begins with data.
The Data comes from PAT
It matures through learning.

PAT provides the data foundation for DSP 2.0.



MEASURE → **UNDERSTAND** → **MODEL** → **CONTROL** → **RELEASE**

in development | the process | what matters | what is proven | with confidence

WHERE WILL

YOU START?

TRY3i here to support
Contact andrew@try3i.com introductory call

Improve what works. Intensify what matters. Innovate what comes next.