Systems Technology in Pharmaceutical and Biologics QbD Implementation

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Background on QbD approach

Process development involves:

- Define the target product profile
- Identify the critical quality attributes (CQAs)
- Select an appropriate manufacturing strategy
- Implement a control strategy

This talk is on control systems technology for integrated pharmaceutical and biologics manufacturing

Why Integrated Manufacturing?

Reduce contact between biology/chemistry & personnel

Continuous operation has the potential to

- Increase product quality
- Increase yields
- Enable new drug product formulations (e.g., thin films)
- Reduce scale-up risks
- Reduce footprint

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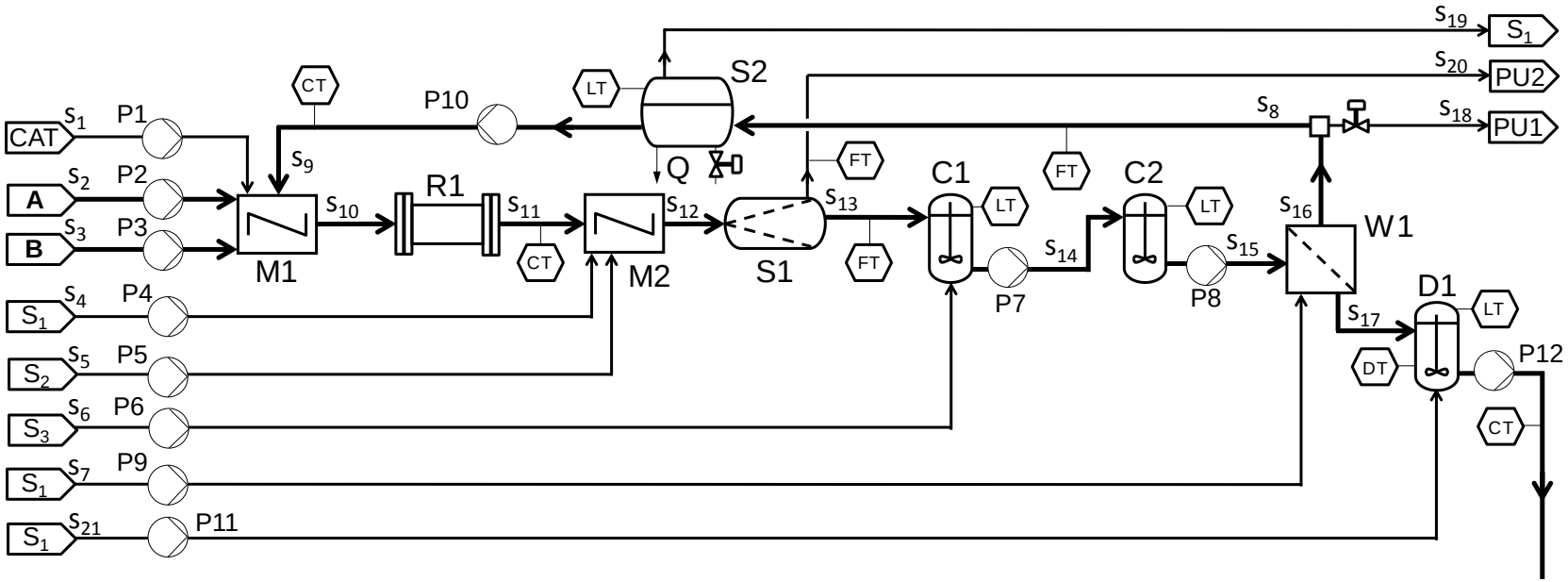
Outline

- Control Systems for Integrated Continuous Operations
- Design Spaces vs. Feedback Control
- Application to Biologics Manufacturing

Integrated Control Strategy for Continuous Manufacturing



- Tight integration of continuous operations can result in disturbances propagating downstream, unless their effects are suppressed by an integrated control strategy
- The strategy must optimize the overall plant operation instead of only isolated units (i.e., need *plantwide control*)

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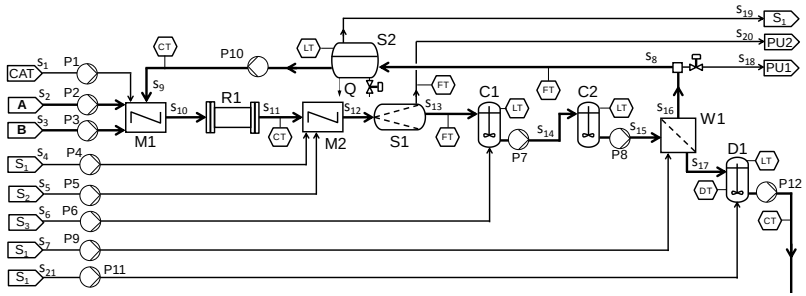
Plantwide Control of Continuous Manufacturing

- Challenges
  - Many connected unit operations
  - Very fast to slow processes
  - Multi-purpose plants with short development time
  - Alignment with regulatory requirements (e.g., design space)



- Approach adapted from the chemical industry
  - Employs systematic and modular design of plantwide control strategies for continuous manufacturing facilities
  - Experimentally demonstrated on continuous pilot plant

R. Lakerveld, B. Benyahia, R.D. Braatz, & P.I. Barton, Model-based design of a plant-wide control strategy for a continuous pharmaceutical plant, *AIChE Journal*, 59, 3671-3685, 2013

A continuous pilot plant

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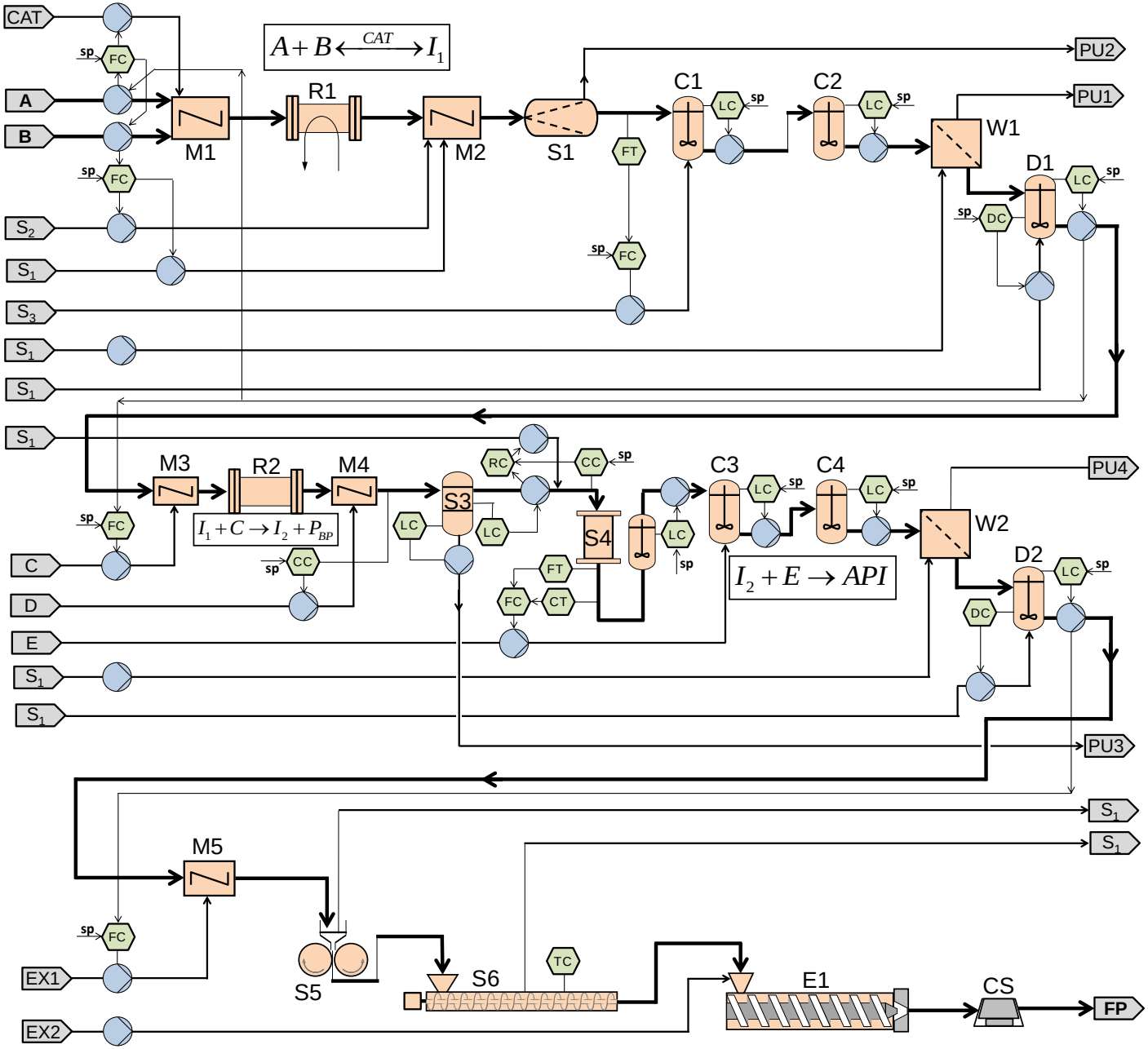
A continuous pilot plant



- First-principles dynamic models were built for each unit operation (UO) as they were developed
- Models were validated and then placed into a plant-wide simulation
- Plant simulation used to design UO & plantwide control strategy

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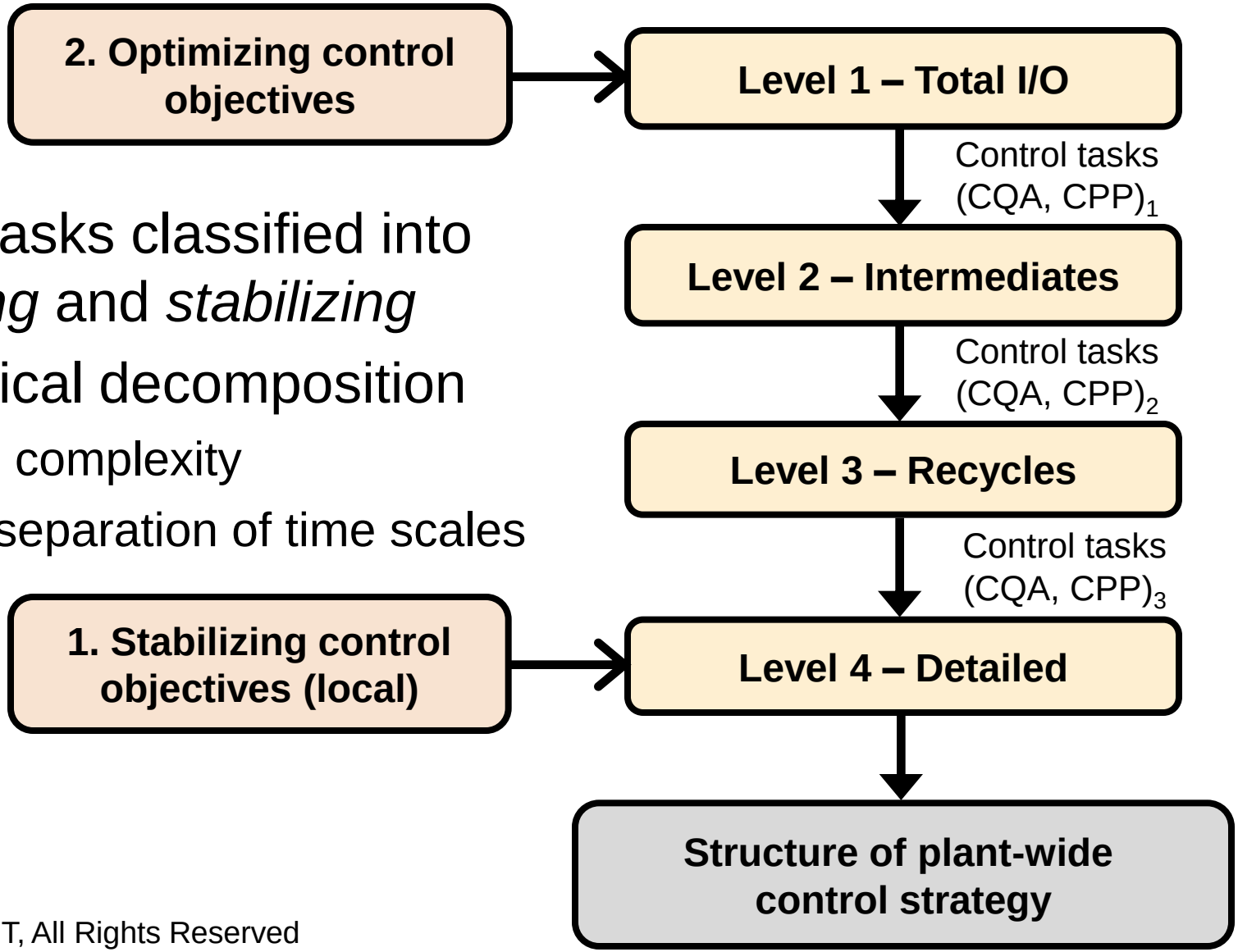
Model-based Design of a Plant-wide Control Strategy

- Control tasks classified into *optimizing* and *stabilizing*
- Hierarchical decomposition
  - Reduces complexity
  - Exploits separation of time scales



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Parametric Sensitivities Used to Evaluate Relationships Between CPPs and CQAs

- Use sensitivities ($S_{i,j}$) to identify causal relations CPPs-CQAs:
  - Direction and order of magnitude
  - Guide selection of automated control loops
  - Determined from process simulation (could use DOE)

$$S_{i,j} = \frac{\partial y_i}{\partial p_j}$$

$$\frac{d}{dt}x(t) = f\left(x(t), u(t), p, t\right), \quad \forall t \in \left(t_0, t_f\right], \quad x\left(t = t_0\right) = x_0,$$

$$y(t) = g\left(x(t), u(t), p, t\right)$$

$$h\left(x(t), u(t), p, t\right) \le 0,$$

$$u_{MV}(t) = K_p\left[\varepsilon(t) + \frac{1}{\tau_I}\int_0^t \varepsilon(\tau)d\tau + \tau_D\frac{d\varepsilon}{dt}\right], \text{ for all feedback control loops}$$

$$\varepsilon(t) = y_{SP} - y_{CV}(t)$$

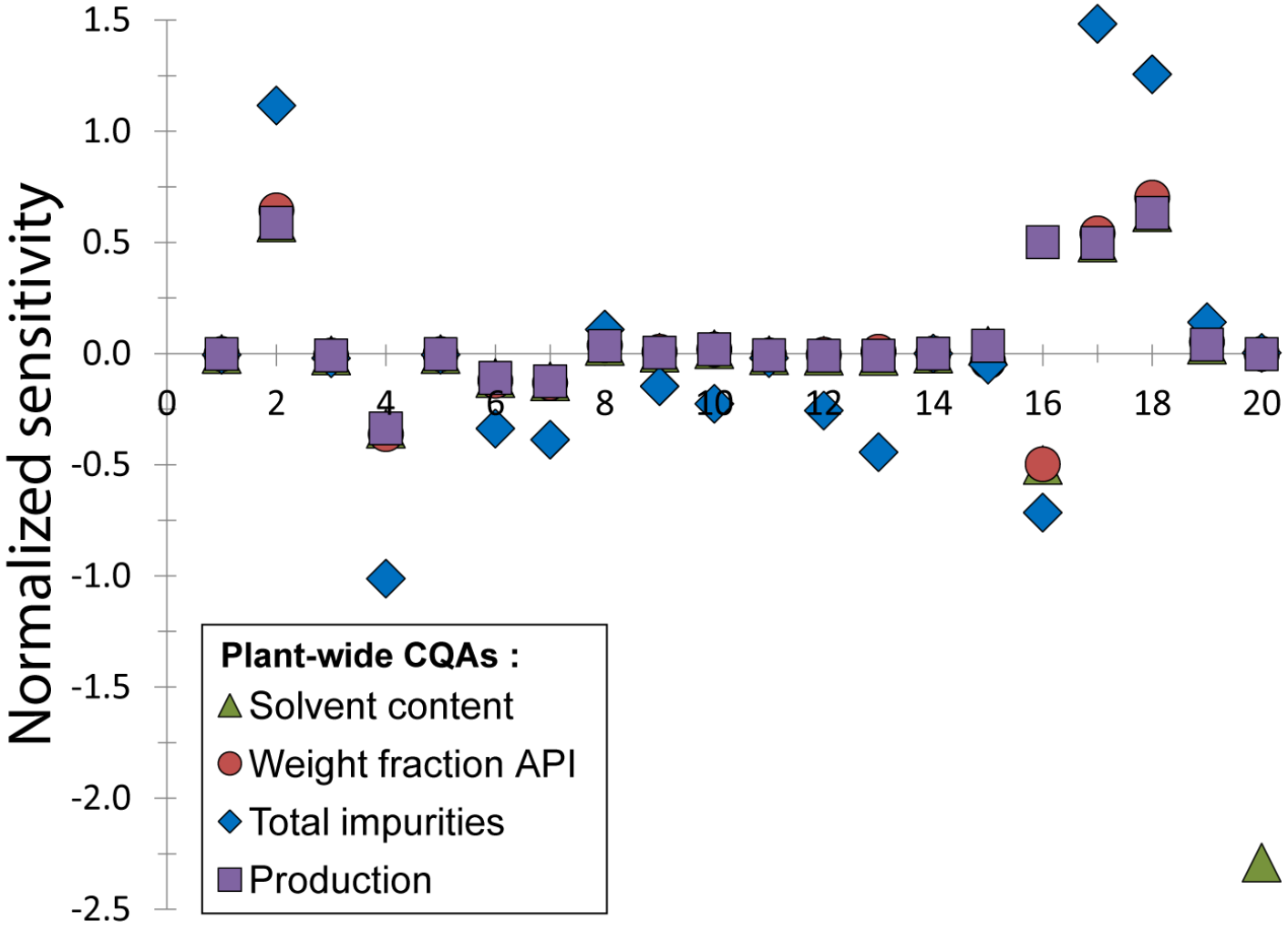
$x(t)$ - State variables

$u(t)$ - Input variables

$y(t)$ - Output variables (CQAs)

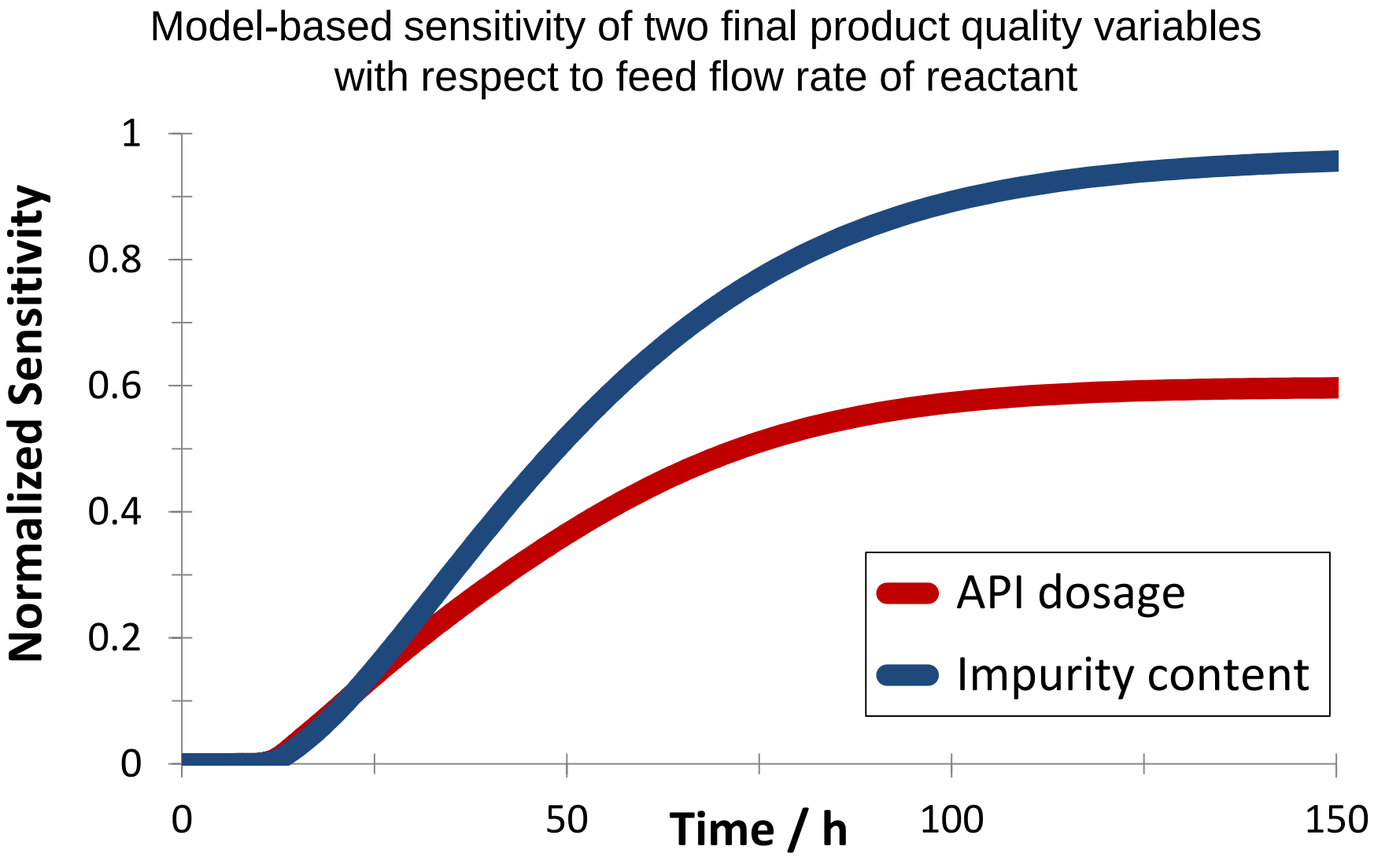
p - Parameters (PPs)

Example Sensitivity Results:
Level 1: Total Inputs & Outputs



PP ID	Type	Stream
1	Flow rate	s1
2	Flow rate	s2
3	Flow rate	s3
4	Flow rate	s4
5	Flow rate	s5
6	Flow rate	s6
7	Flow rate	s7
8	Valve	s18
9	Flow rate	s21
10	Flow rate	s22
11	Flow rate	s23
12	Flow rate	s24
13	Flow rate	s25
14	Flow rate	s37
15	Flow rate	s38
16	Flow rate	s39
17	Heat input	s19
18	Purity	s2
19	Purity	s3
20	Flow rate	s46

Also use sensitivities to evaluate dynamic I/O relationships, to assess controllability and disturbance propagation



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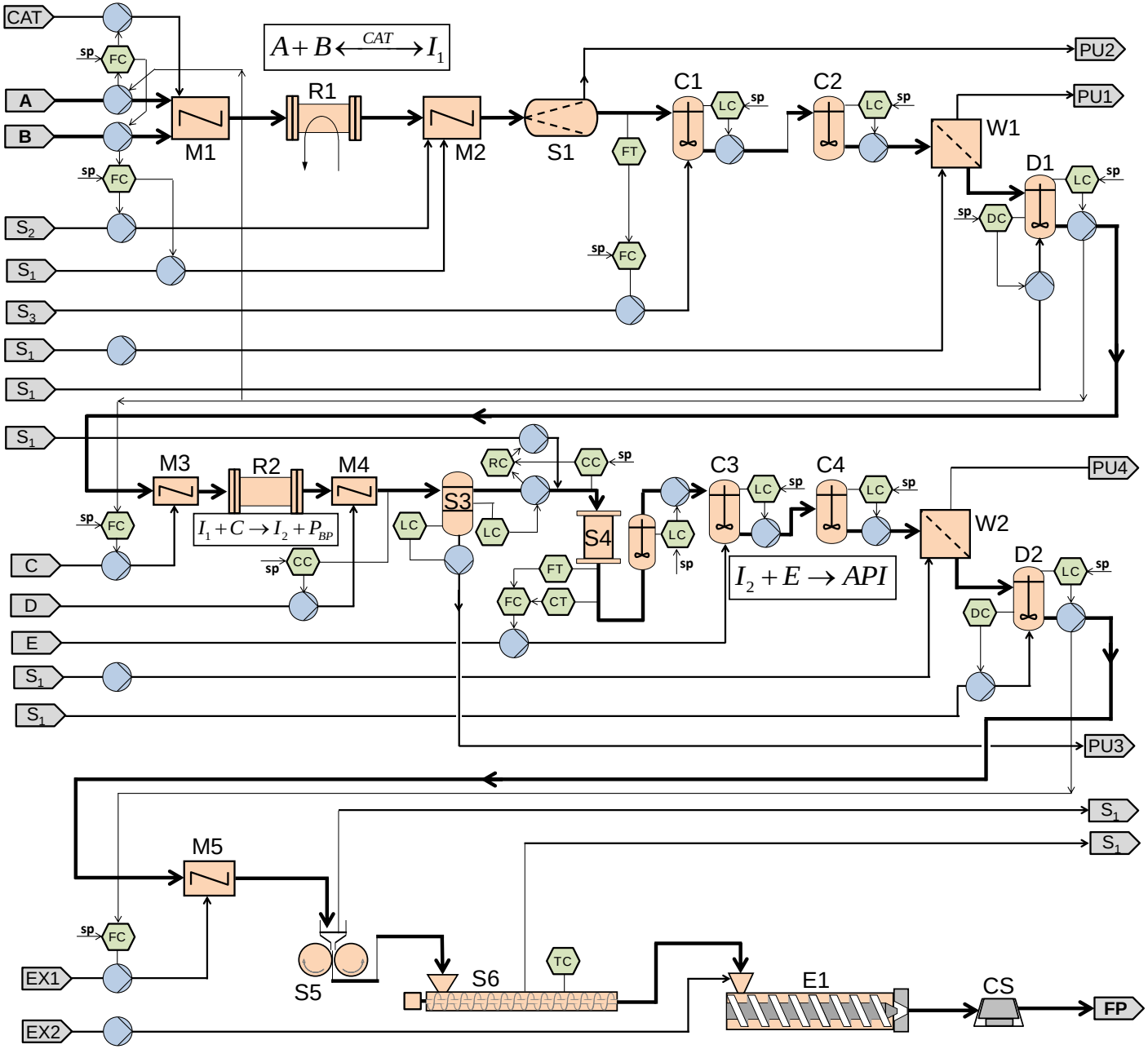
A continuous pilot plant



Met all purity specs in Summer 2012

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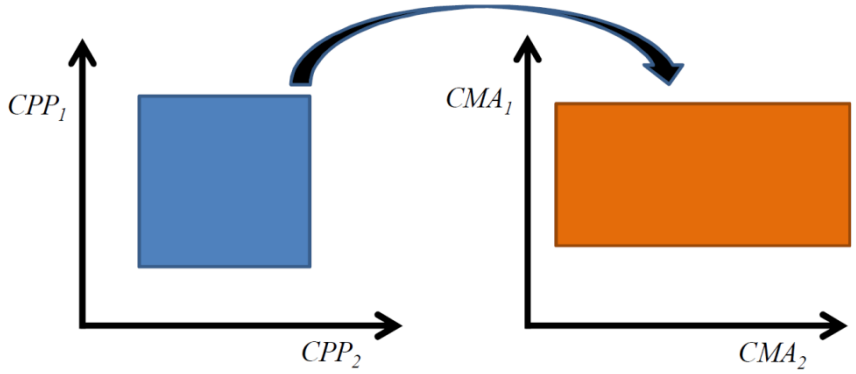
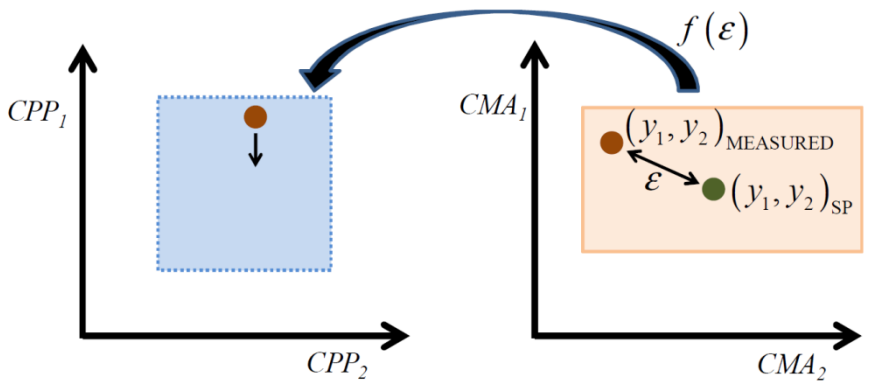
Design Space vs. Feedback Control (both are consistent with quality-by-design principles)





- Design-space methods:
  - Control strategy based on operation within a fixed parameter space
  - Applicable to each continuous process unit operation
  - More complicated to apply to an entire continuous pharmaceutical manufacturing plant

- Feedback methods:
  - Control strategy based on feedback *to* a "parameter space"
  - Easier to scale up
  - Design space does not need to be exhaustively validated a priori
  - Necessary for continuous manufacturing

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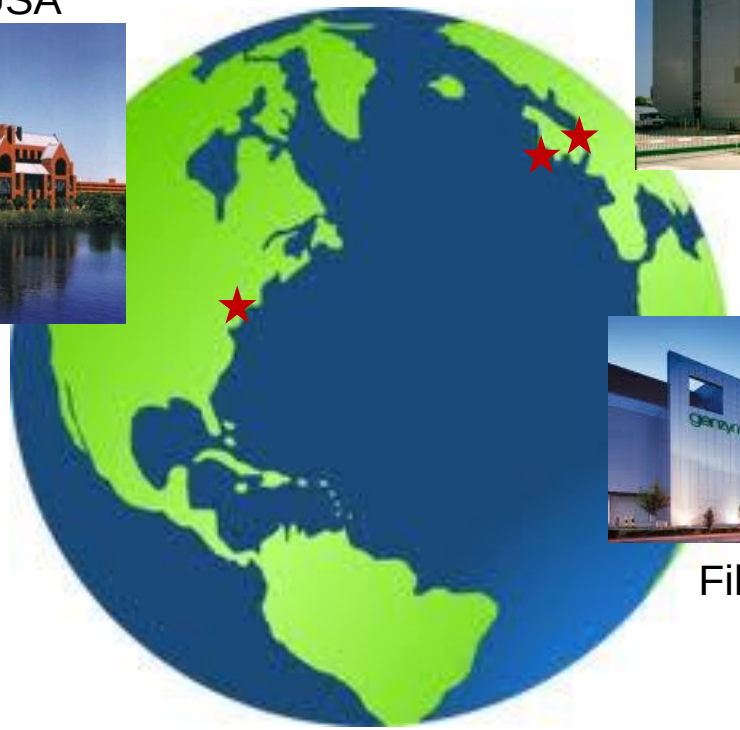
Manufacturing biologic drugs today

Product QC: Haverhill, UK

Product manufacturing:
Allston, MA USA

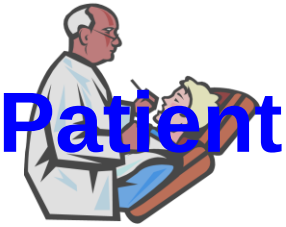


Fill/finish: Waterford, IE

Cerezyme patients distributed worldwide

Towards Biomanufacturing on Demand (BioMOD)

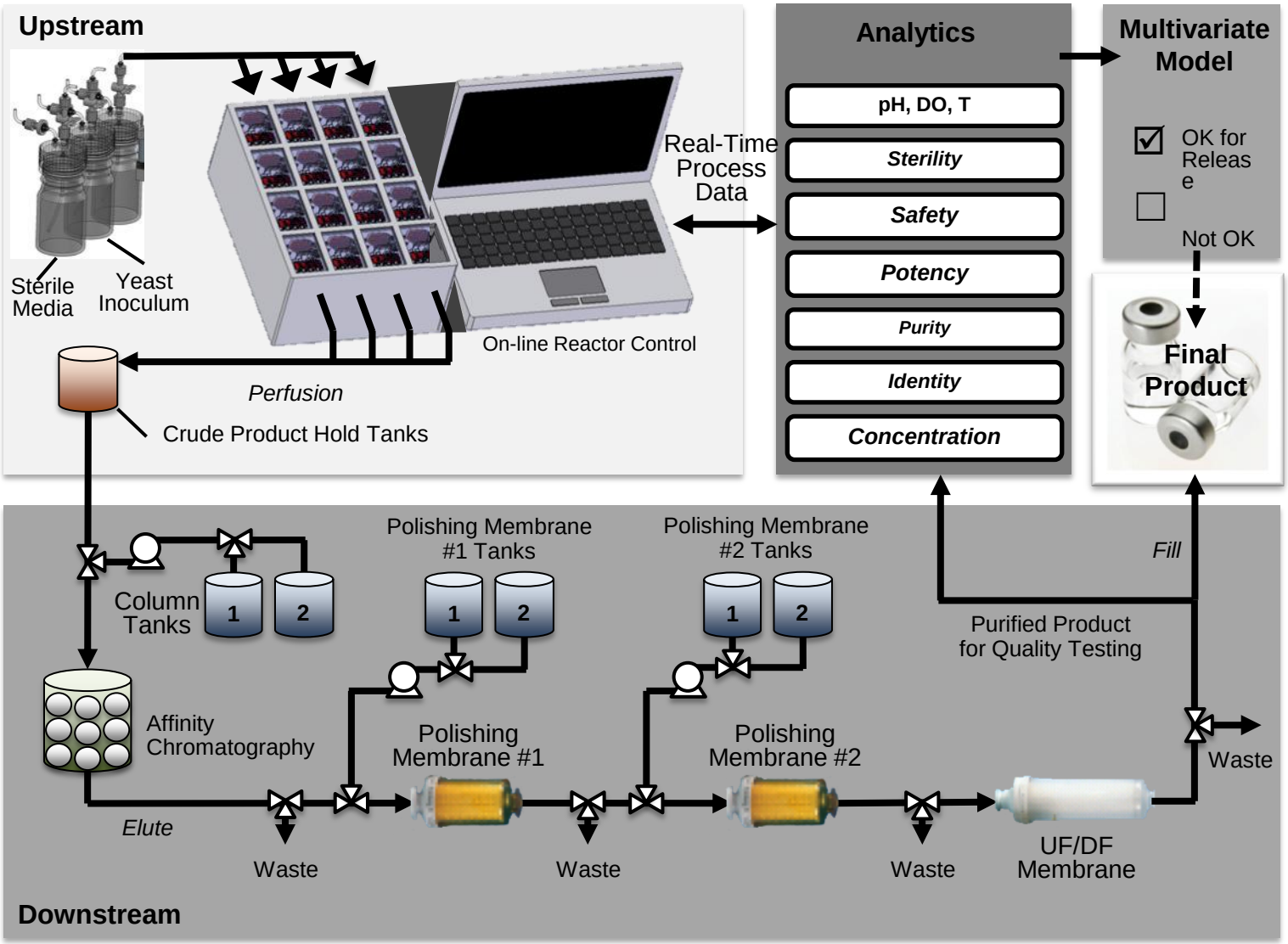
Design ← Requirements ← Patient



BioMOD capabilities

- Enable flexible methodologies for genetic engineering/modification of microbial strains to synthesize multiple and wide-ranging protein-based therapeutics
- Develop flexible & portable device platforms for manufacturing multiple biologics with high purity, efficacy, and potency, at the point-of-care, in short timeframes (**<24 hours**), when specific needs arise
- Include end-to-end manufacturing chain (including downstream processing) within a microfluidics-based platform
- Focus on currently approved therapeutics by FDA (i.e. no drug discovery)

Integrated and Scalable Cyto-Technology (InSCyT) biomanufacturing platform



Rationale for *Pichia pastoris* as microbial host for biosimilar products

Advantages from a regulatory perspective

- Many products on market or in late-stage development (including one Phase I target)
- Reduced risk for viral contamination in InSCyT process
- Human-like post-translational modifications (folding, glycosylation, etc.)

Technical benefits

- Genetically stable organism
- High density cultivation (culture volume >70% biomass)
- High yields of secreted proteins (up to ~15 g/L)
- Limited host cell protein (HCP) profile (eases burden on downstream)
- Amenable to lyophilization

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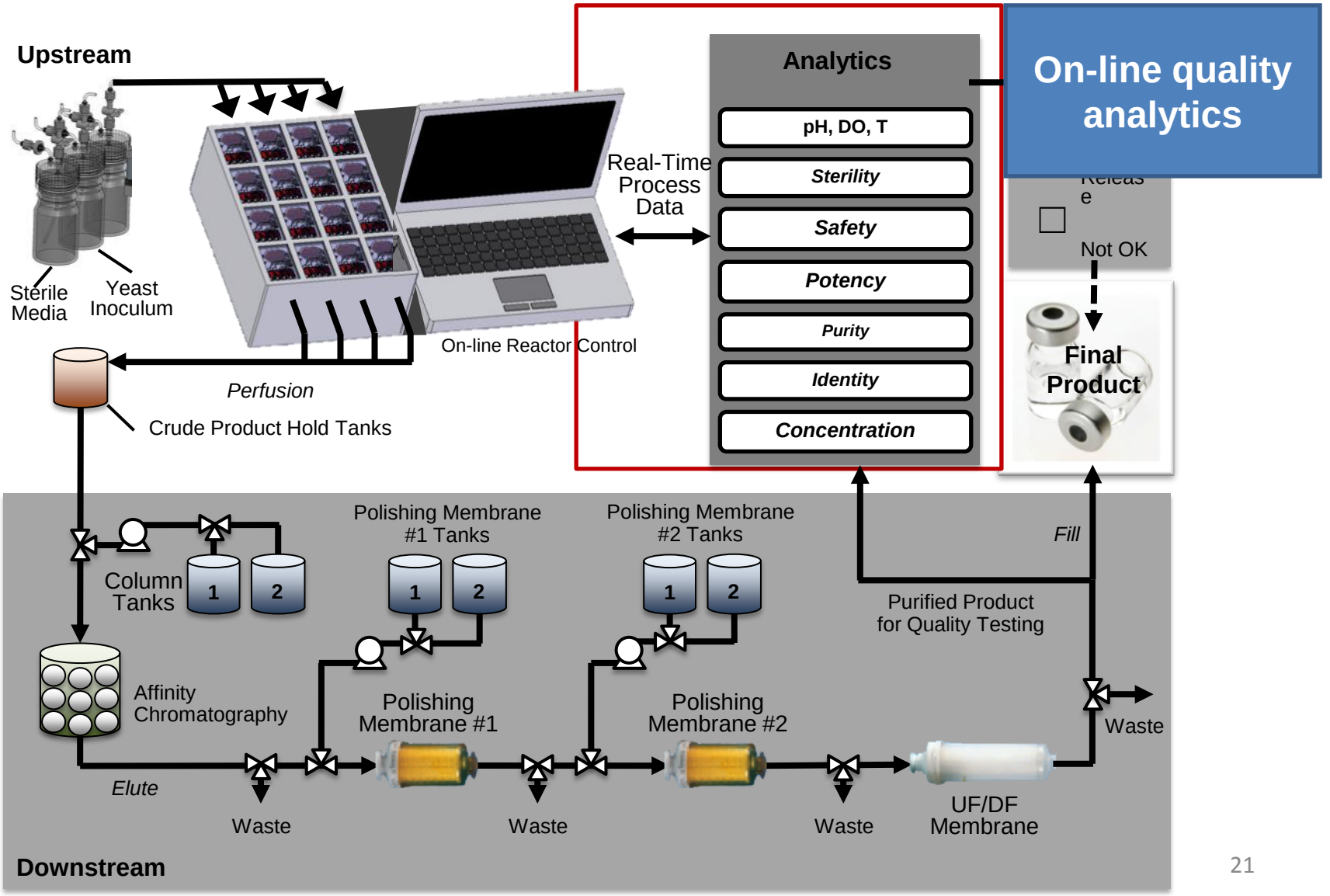

Recall Quality by Design approach

Process development involves:

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- Select an appropriate manufacturing strategy
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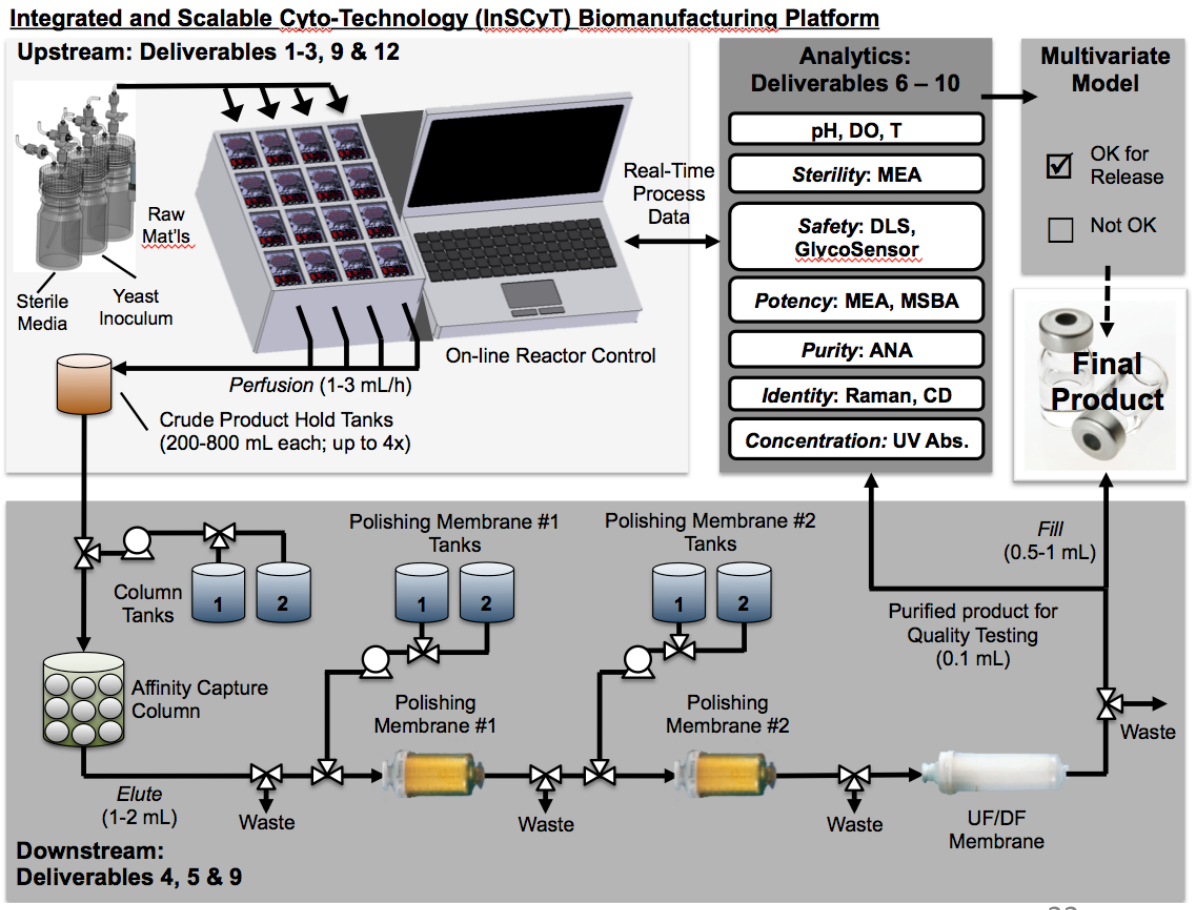
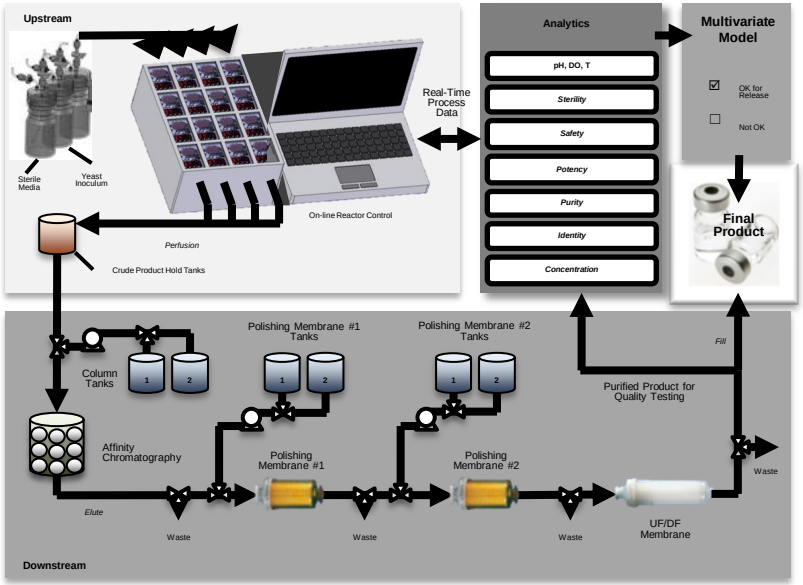


Plant-wide control approach

- Characteristics of InSCyT
  - Many connected unit operations
  - Many discrete operations
  - Multi-product plant
  - Alignment with regulatory requirements (e.g., design space)

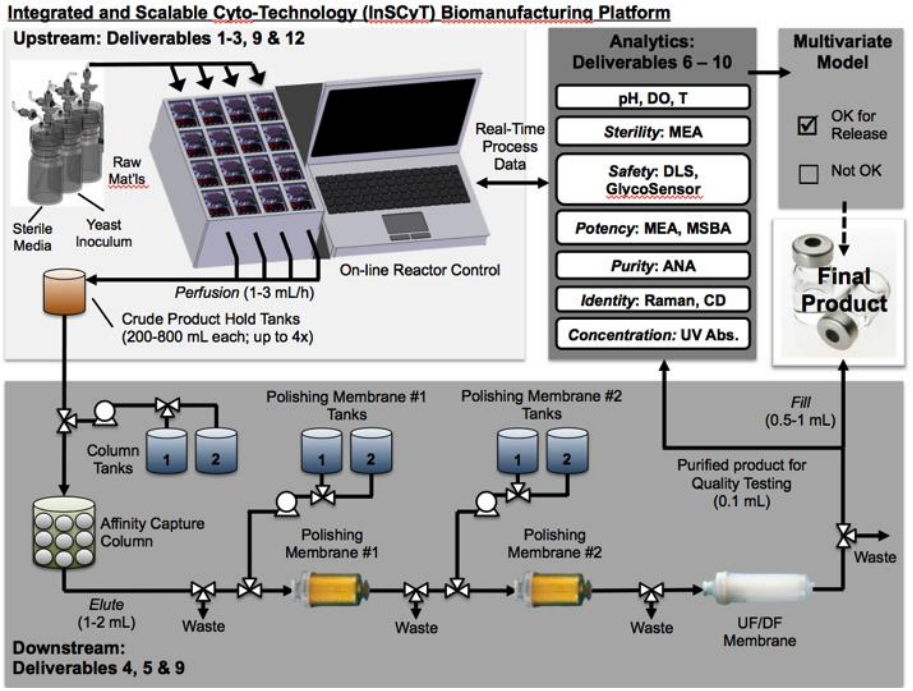


- QbD approach adapted from chemical industry
  - Employing systematic and modular design of plantwide control strategies for production-scale manufacturing facilities
  - Using numerical algorithms that can handle discrete operations and multiple products

R. Lakerveld, B. Benyahia, R.D. Braatz, & P.I. Barton, Model-based design of a plant-wide control strategy for a continuous pharmaceutical plant, *AIChE Journal*, 59, 3671-3685, 2013

Application to biologic drug production

- Build first-principles dynamic models for each unit operation (UO)
- Design control system for each UO to meet "local" material attributes
- Evaluate performance in simulations and propose design modifications as needed



- Implement and verify the control system for each UO
- Design and verify plantwide control system to ensure that the CQAs are met

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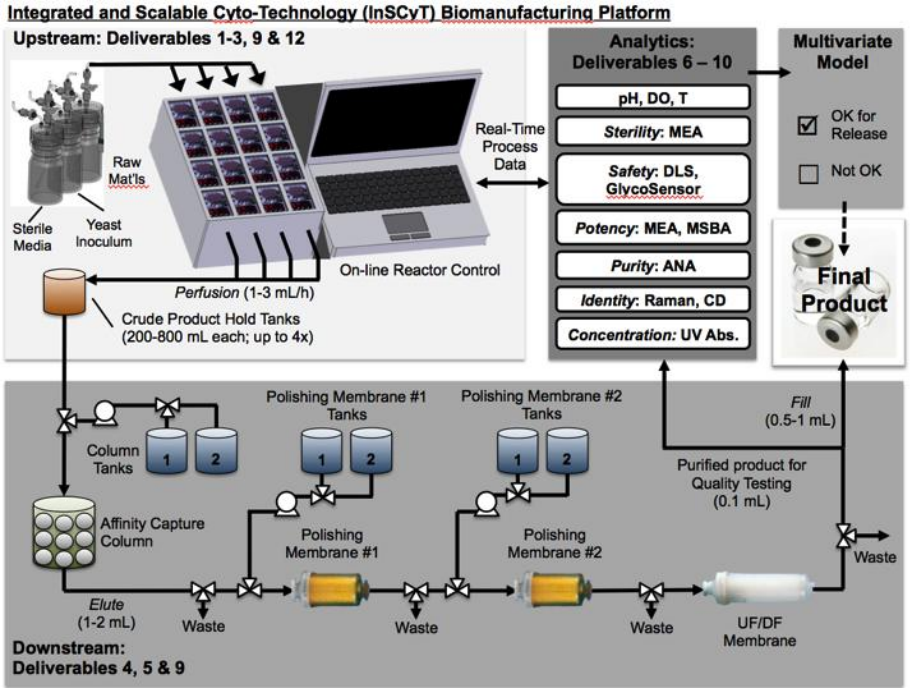

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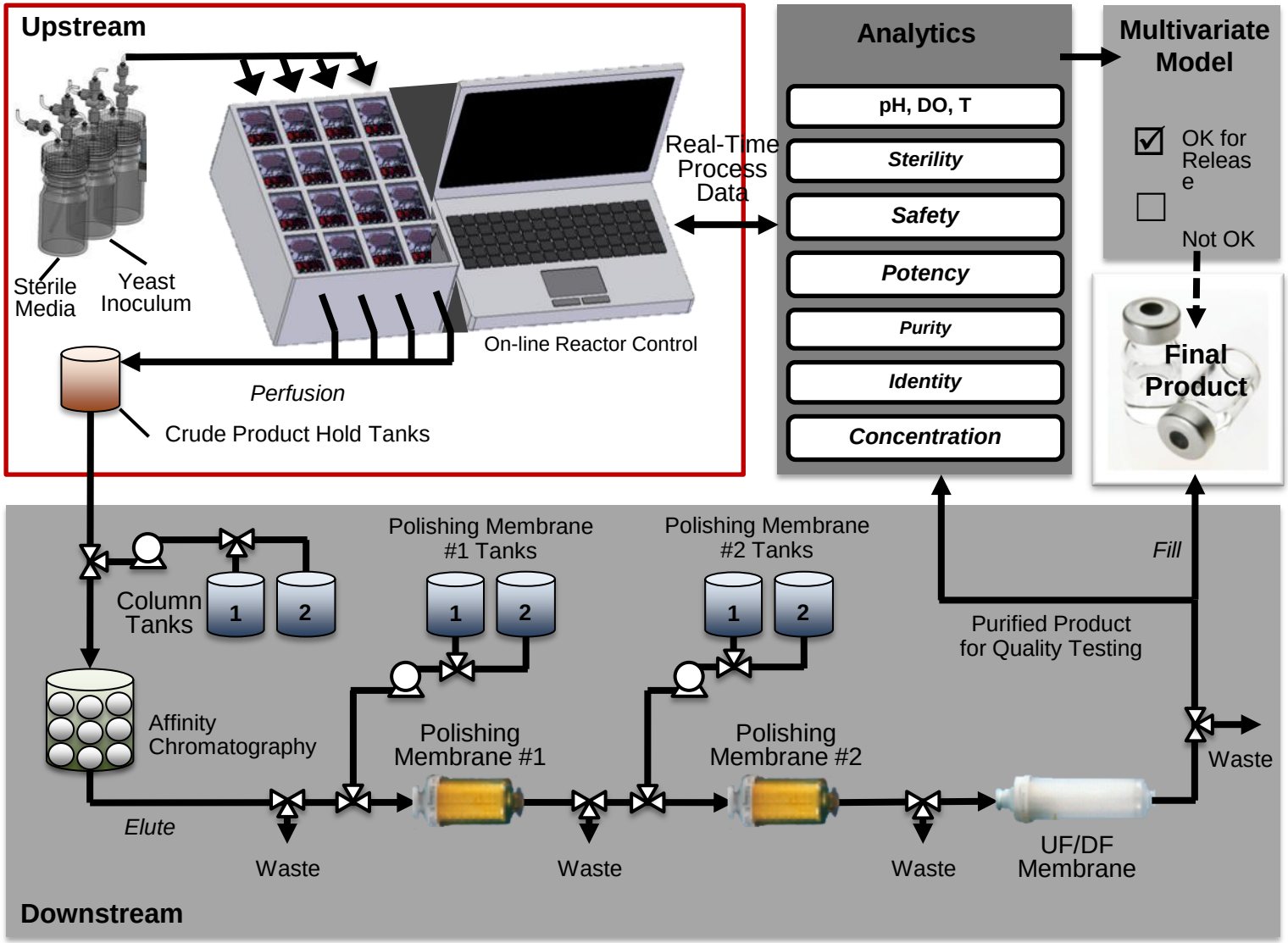
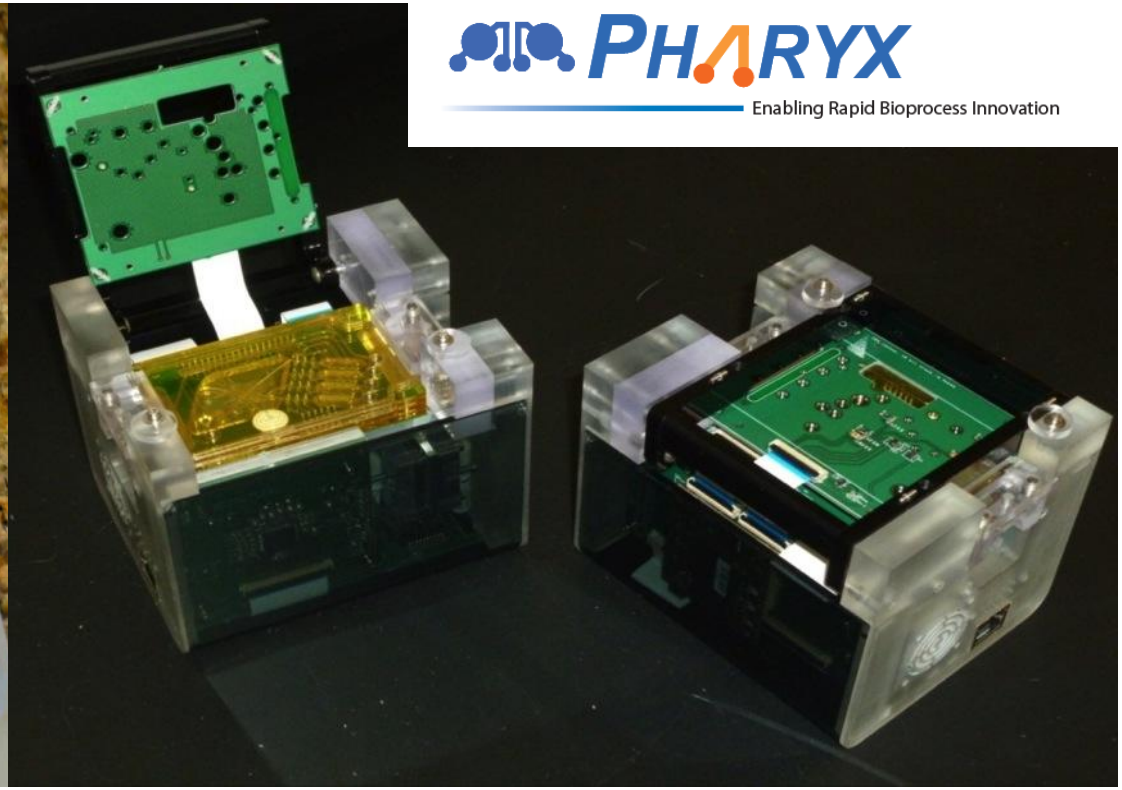
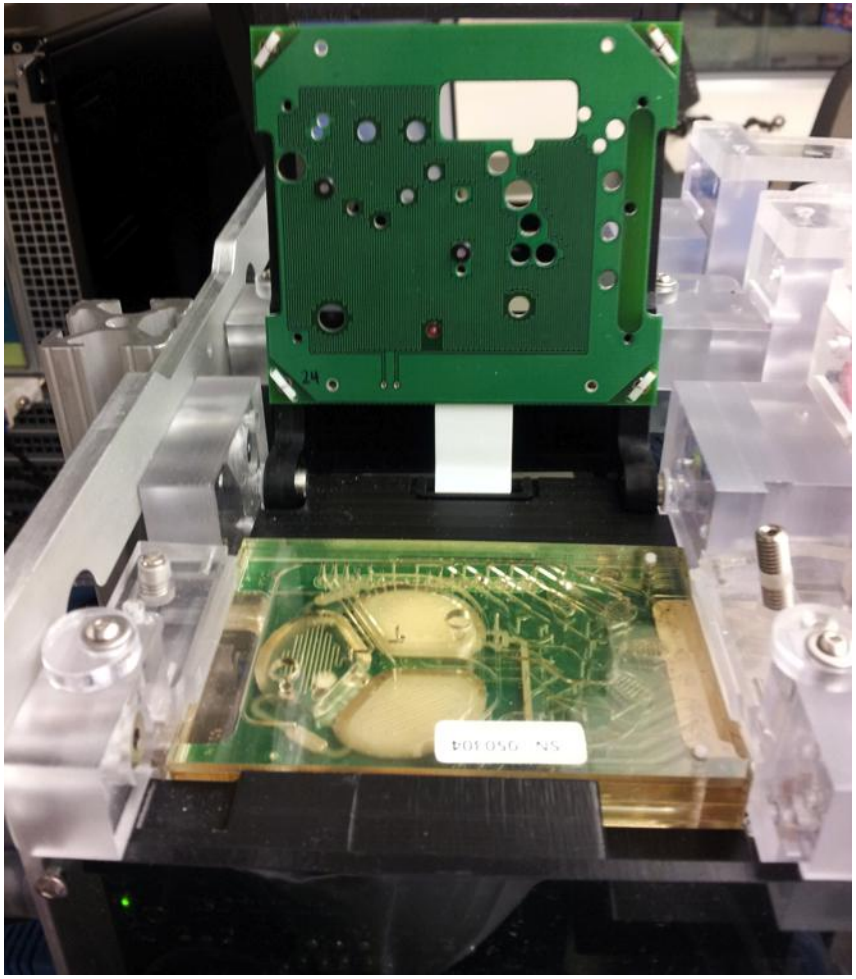


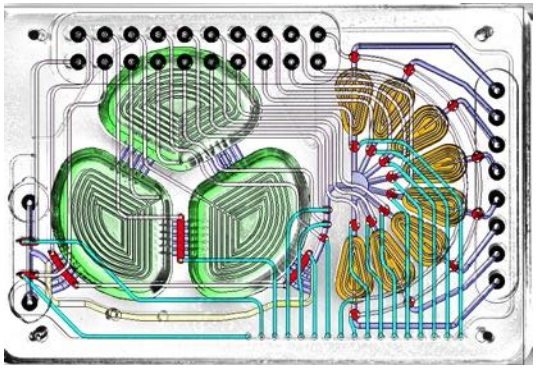
Local “UO” control for bioreactor unit operations



PHARYX
Enabling Rapid Bioprocess Innovation

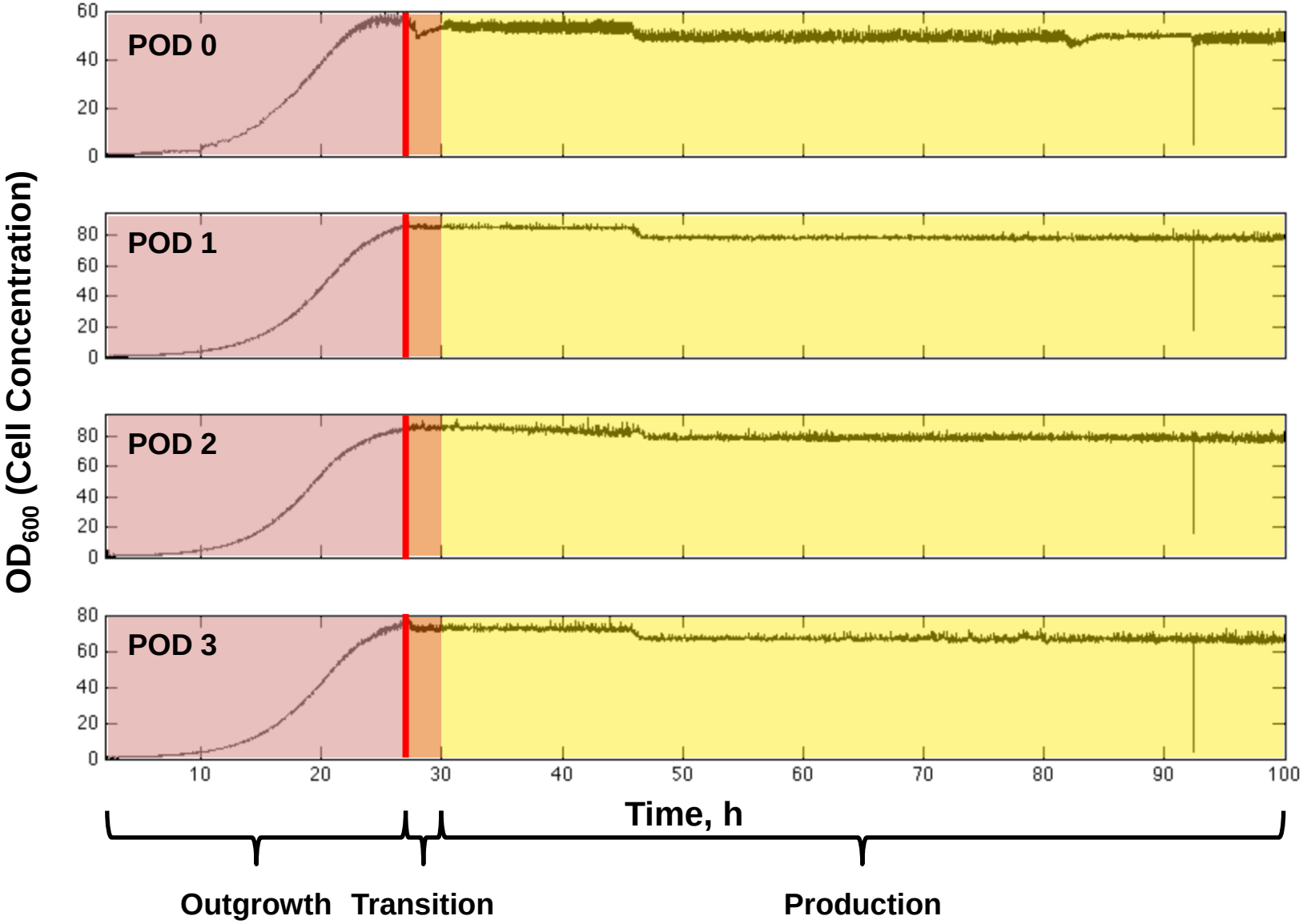
Local “UO” Control: Microscale controlled cell culture





Kevin S. Lee et al., *Lab on a Chip*, 11, 1730-1739 (2011)

Reproducible microbioreactor cultivations



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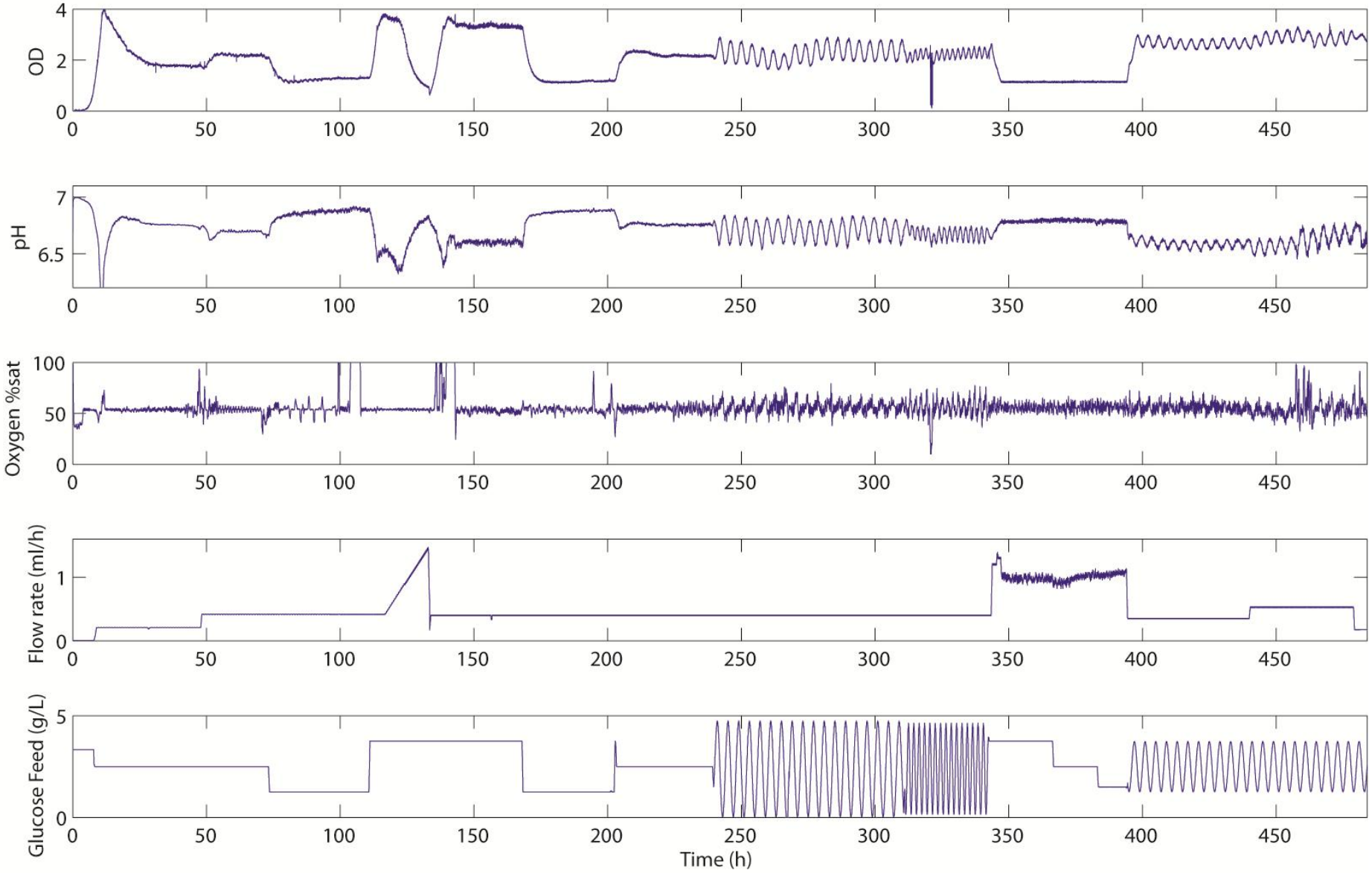

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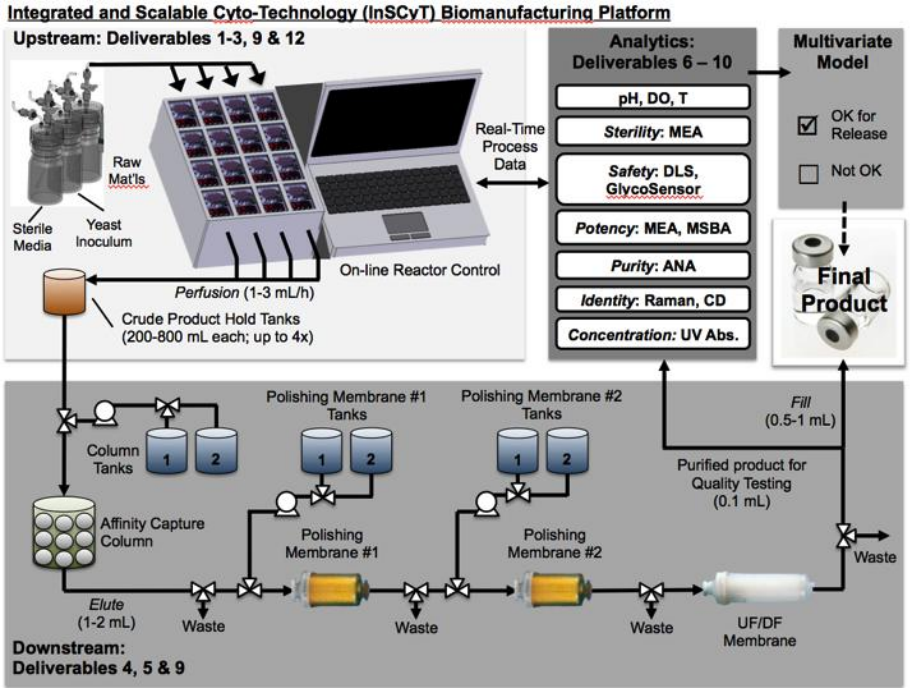

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