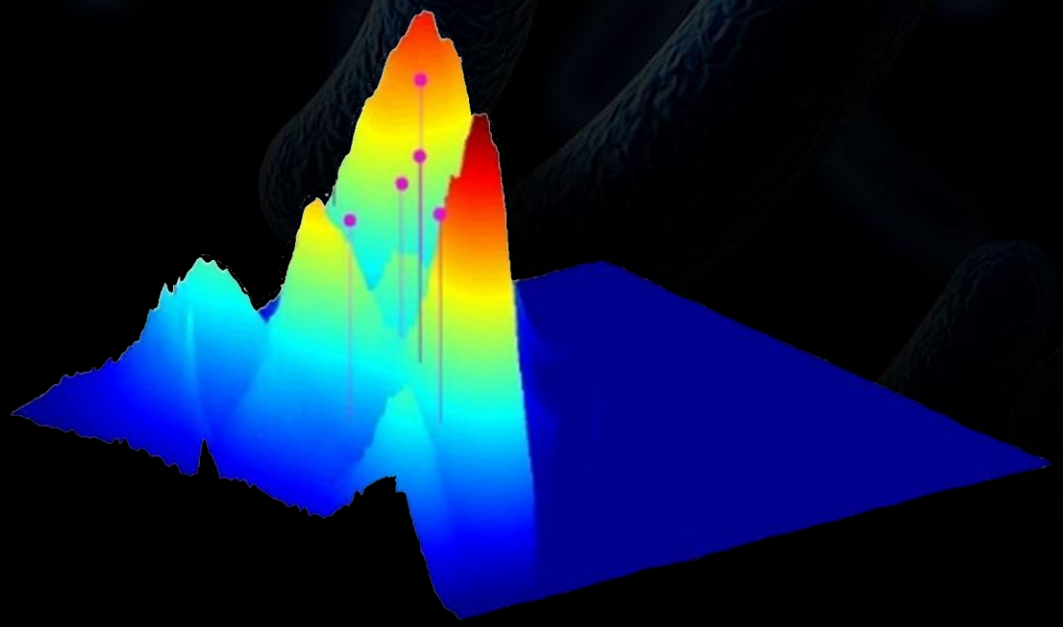
From Spectra to Insights: Machine Learning and Neural Networks for Optical Signature Detection in Monitoring Industrial Fermentations



Renaud Barriere, Christopher Jean, Alexis Dauth, and Joel Sirois, P.Eng. PhD
Professor
Biotechnological Engineering
UdS Université de Sherbrooke

Founder-CEO
BioIntelligence

Biomanufacturing

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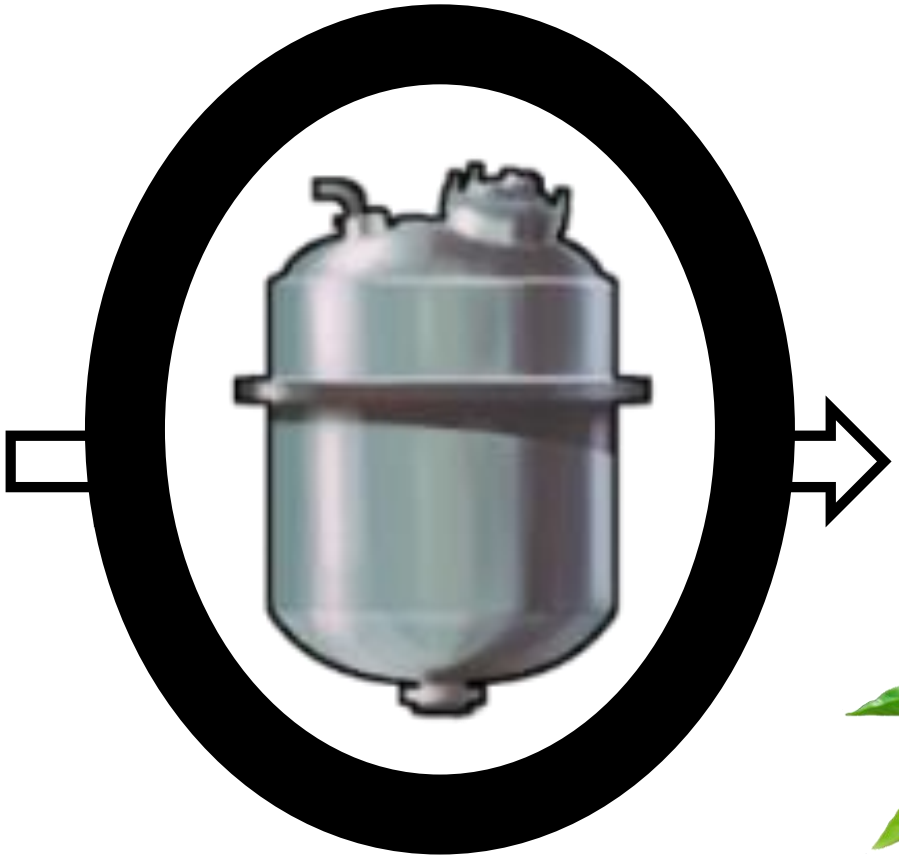
Biomanufacturing



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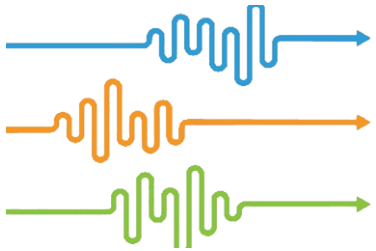
No (Live) Monitoring = Delays = Losses

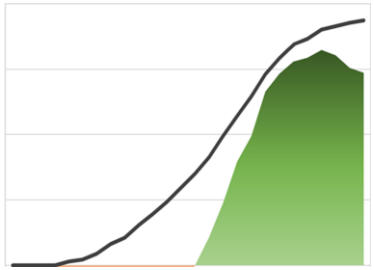
- Nutrients deprivation
- Process deviations
- Contaminations

LOSSES IN PRODUCTS & LOWER CONVERSION YIELDS



- Natural variability vs Process variability

VARIABILITY IN RESULTS



- Time to stop/add/change/DSP
- Profitability ≠ [Product]

LOSSES IN PROFITS

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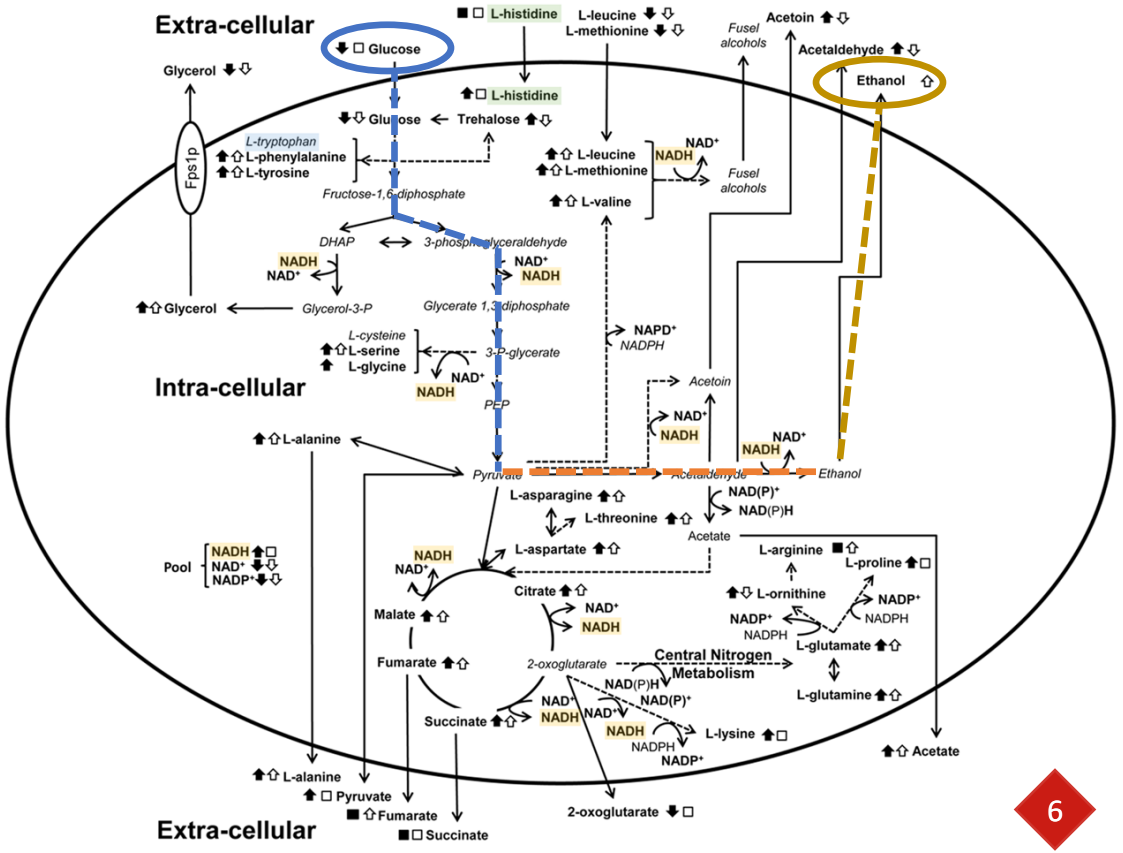
Consumption of nutrients → Biosynthetic pathways → Synthesis of bioproducts



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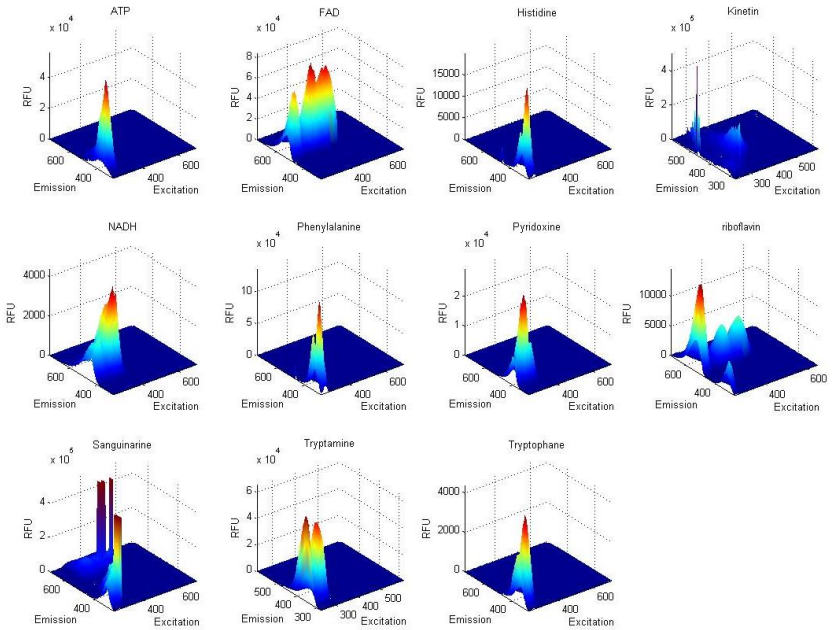
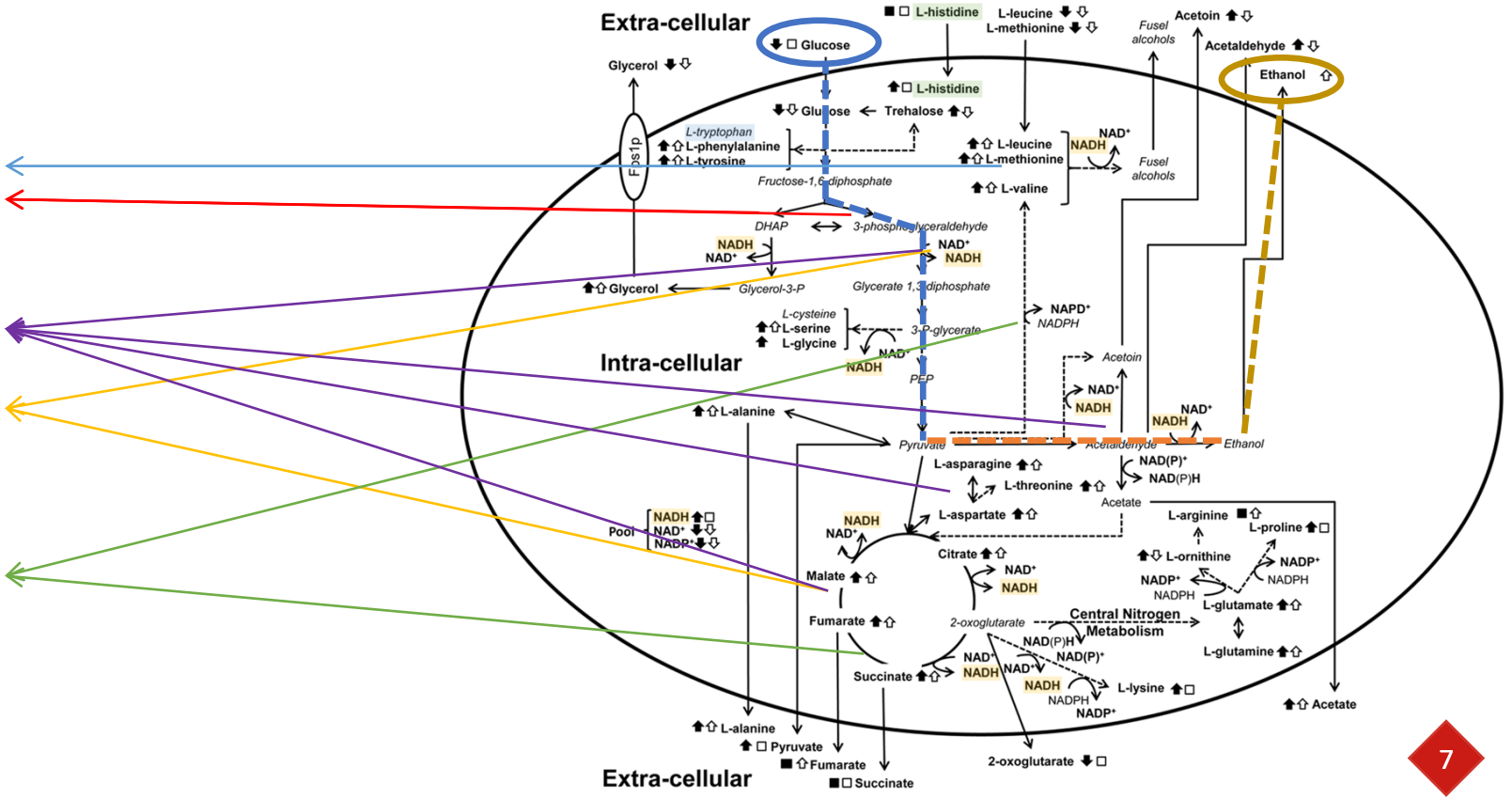
Native fluorescing molecules = Embedded sensors





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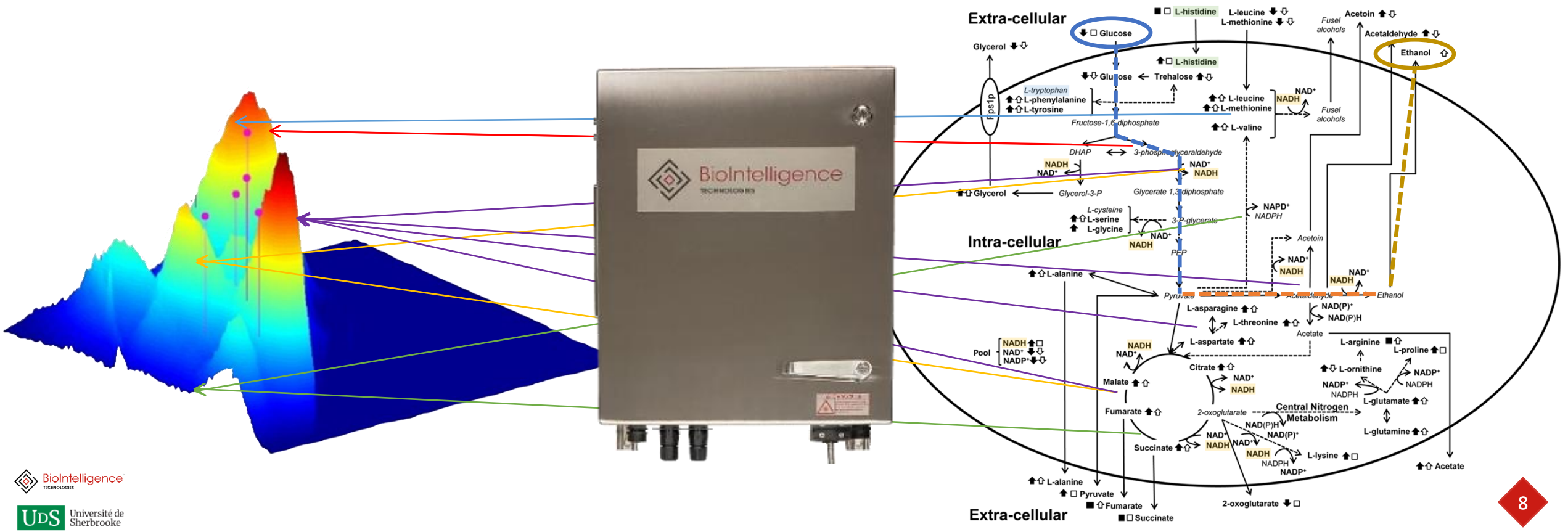
Native fluorescing molecules = Embedded sensors



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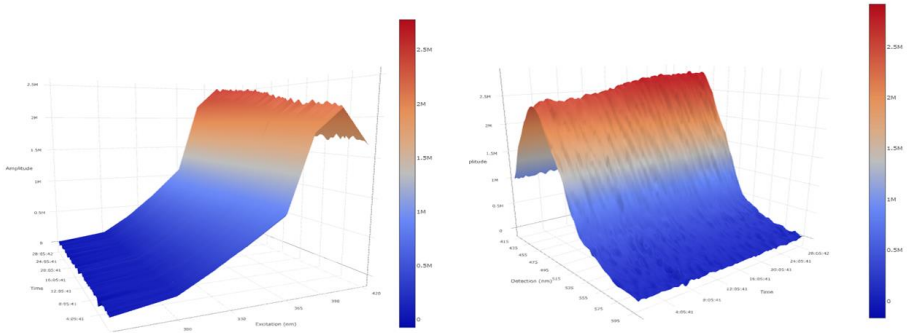
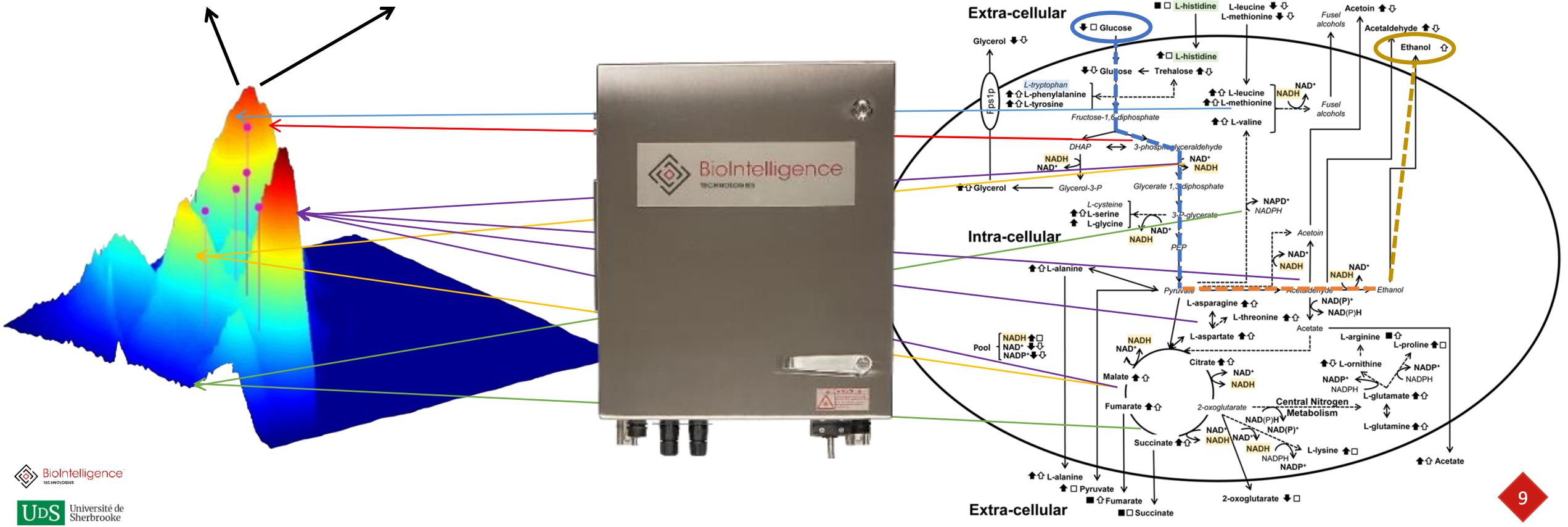
Native fluorescing molecules = Look at Live chemodynamics





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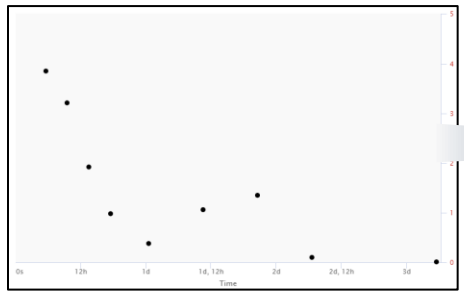
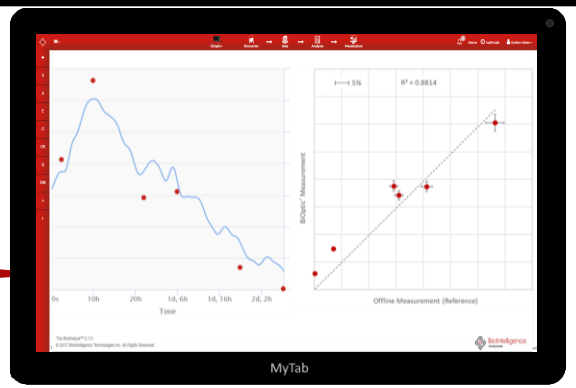
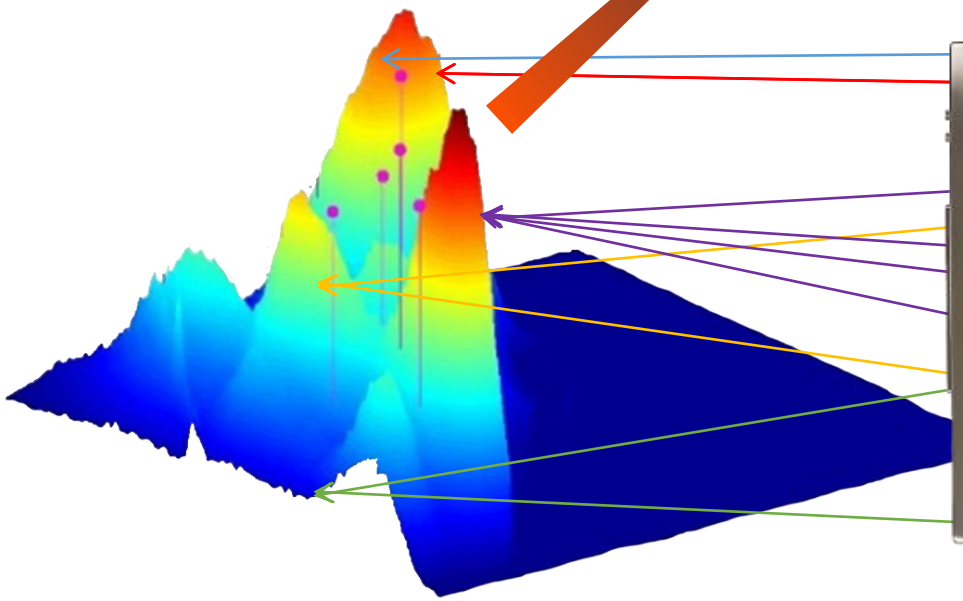
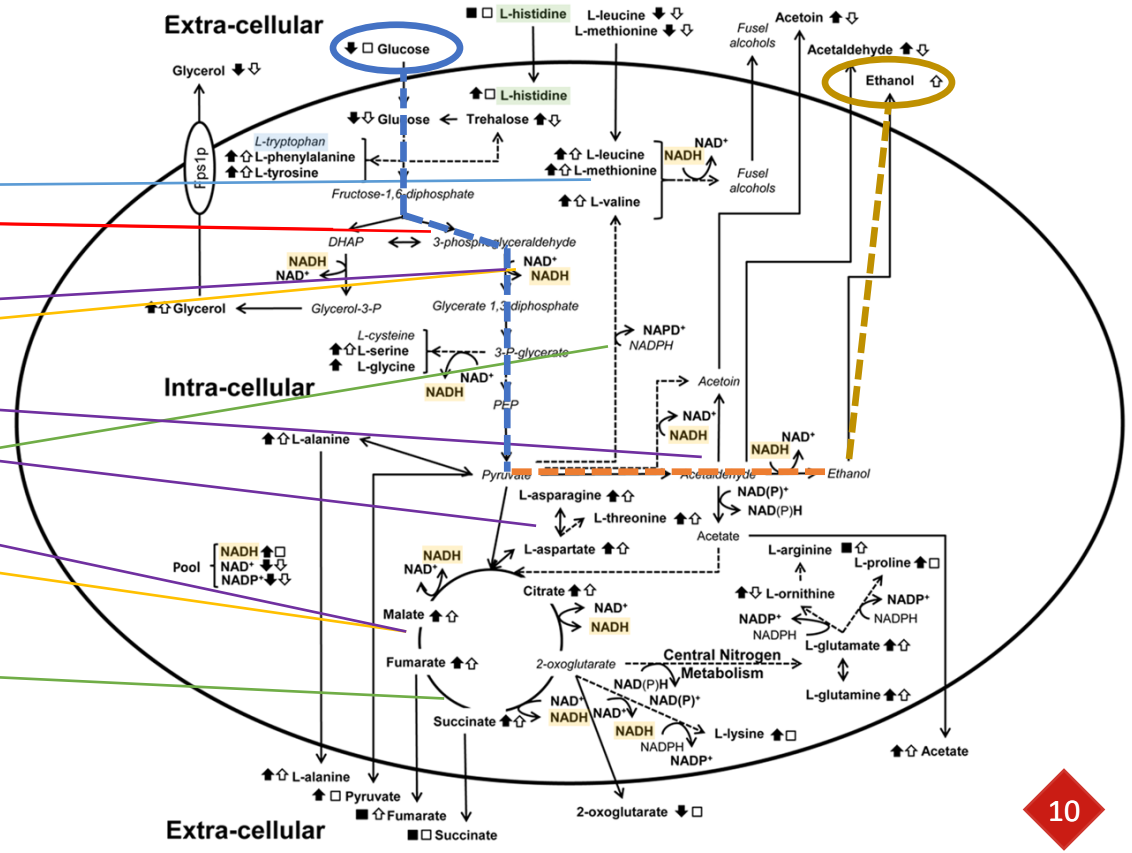
Live fluorescence → Inline monitoring









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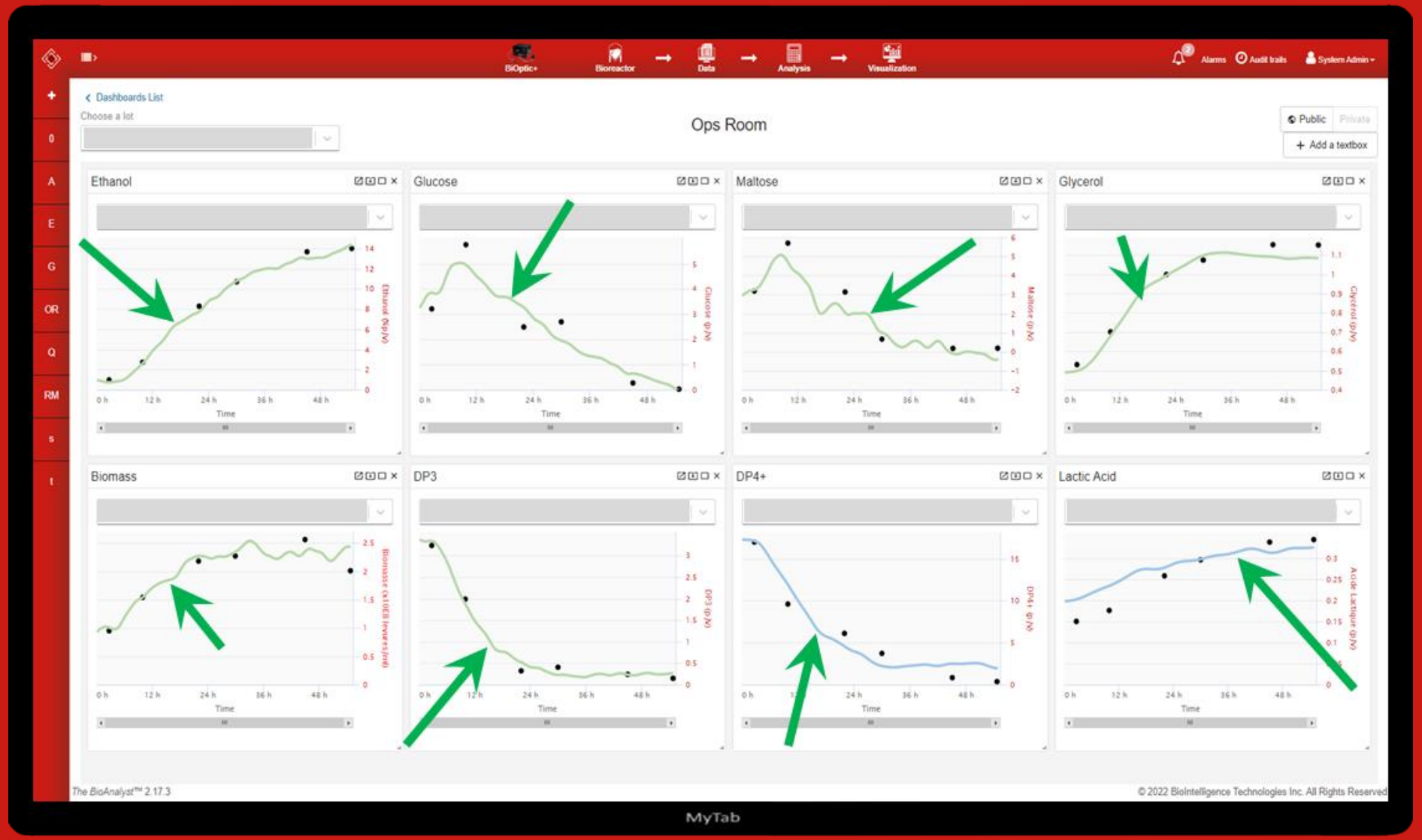
Case Study #1:

Multivariate monitoring ….



100%

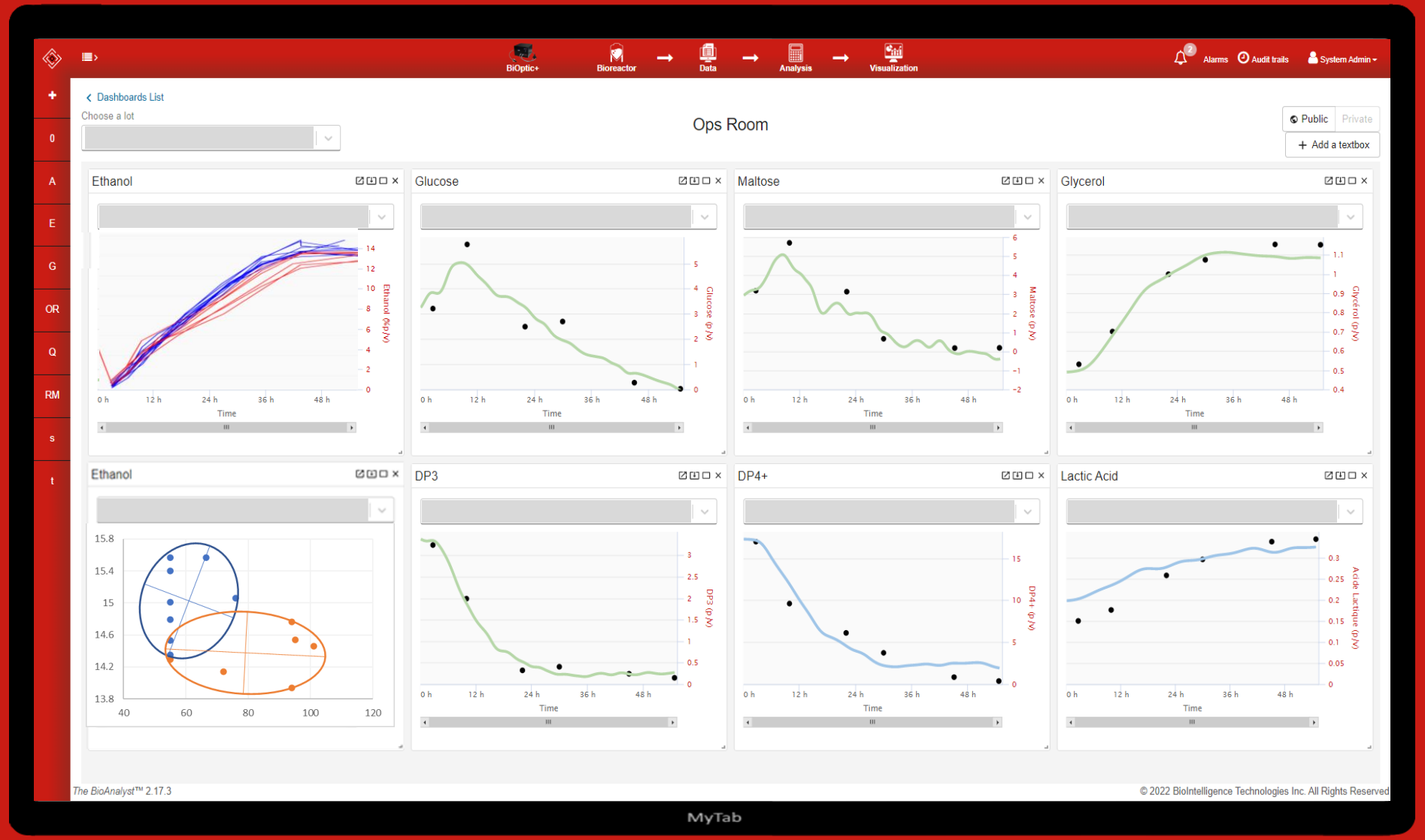
BIOETHANOL
INDUSTRIAL PRODUCTION

27

FERMENTATION
VARIABLES MONITORED

Case Study #1:

Multivariate monitoring enabled to eliminate a slow drift in production, with a **33x ROI/Payback**



100%

BIOETHANOL INDUSTRIAL PRODUCTION

27

FERMENTATION VARIABLES MONITORED

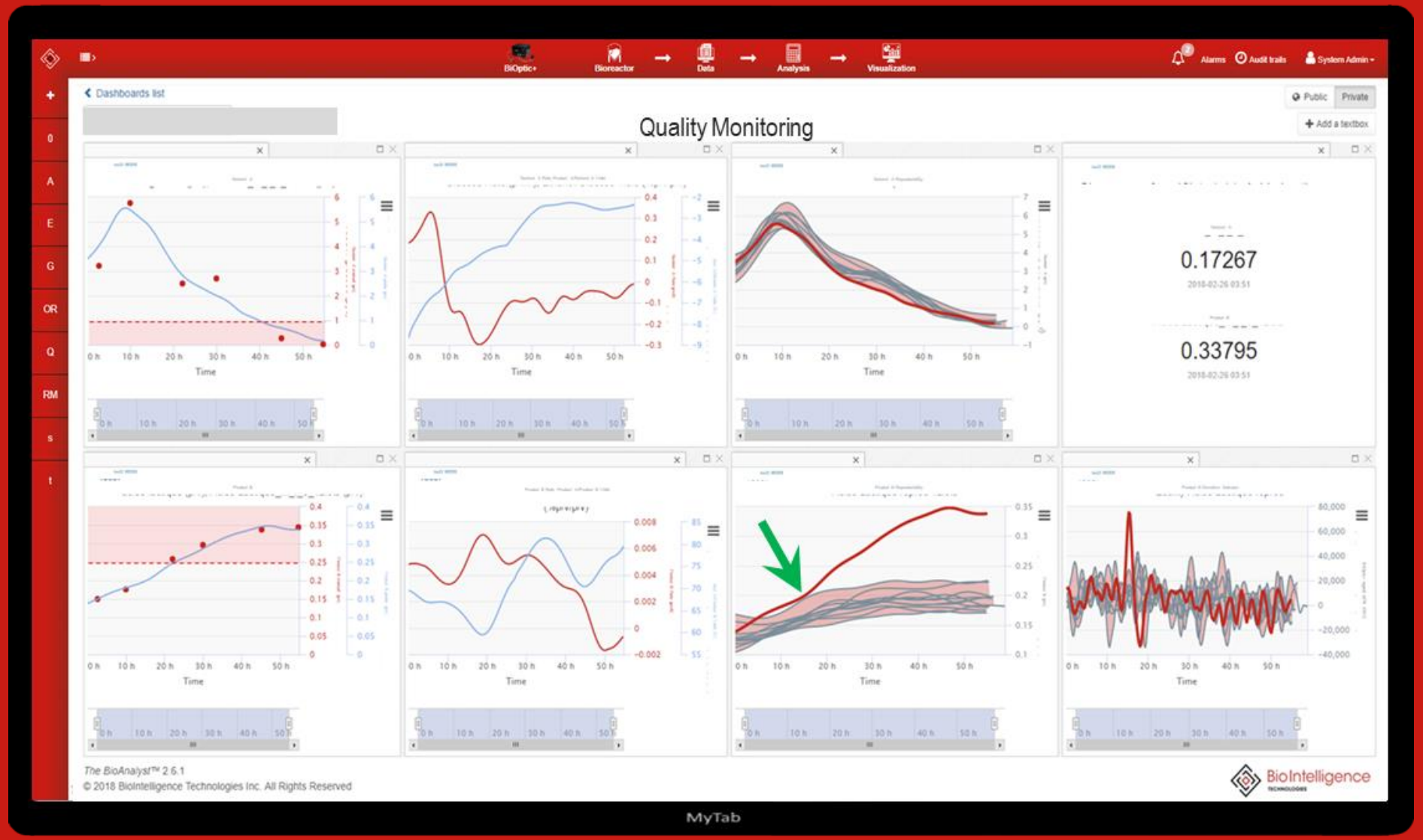
EARLY DETECTION OF LOSSES

33x ROI

1.5 WEEK PAYBACK TIME

Case Study #2:

Early identification of a contamination at full-scale led to estimated savings of $10,000/batch



100%

BIOETHANOL INDUSTRIAL PRODUCTION

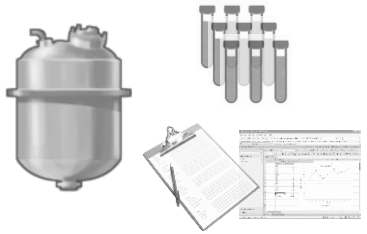
$10k+

ADDITIONNAL SAVINGS/BATCH

EARLY DETECTION OF DEVIATIONS

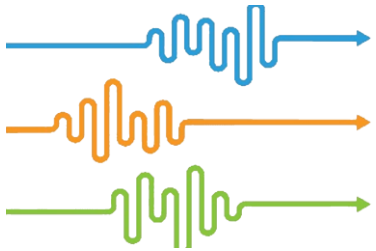
ALARMS TO BE NOTIFIED

No (Live) Monitoring = Delays = Losses



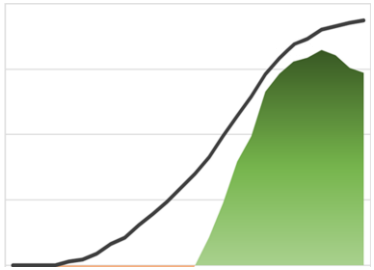
- Nutrients deprivation
- Process deviations
- Contaminations

LOSSES IN PRODUCTS & LOWER CONVERSION YIELDS



- Natural variability vs Process variability

VARIABILITY IN RESULTS



- Time to stop/add/change/DSP
- Profitability ≠ [Product]

LOSSES IN PROFITS

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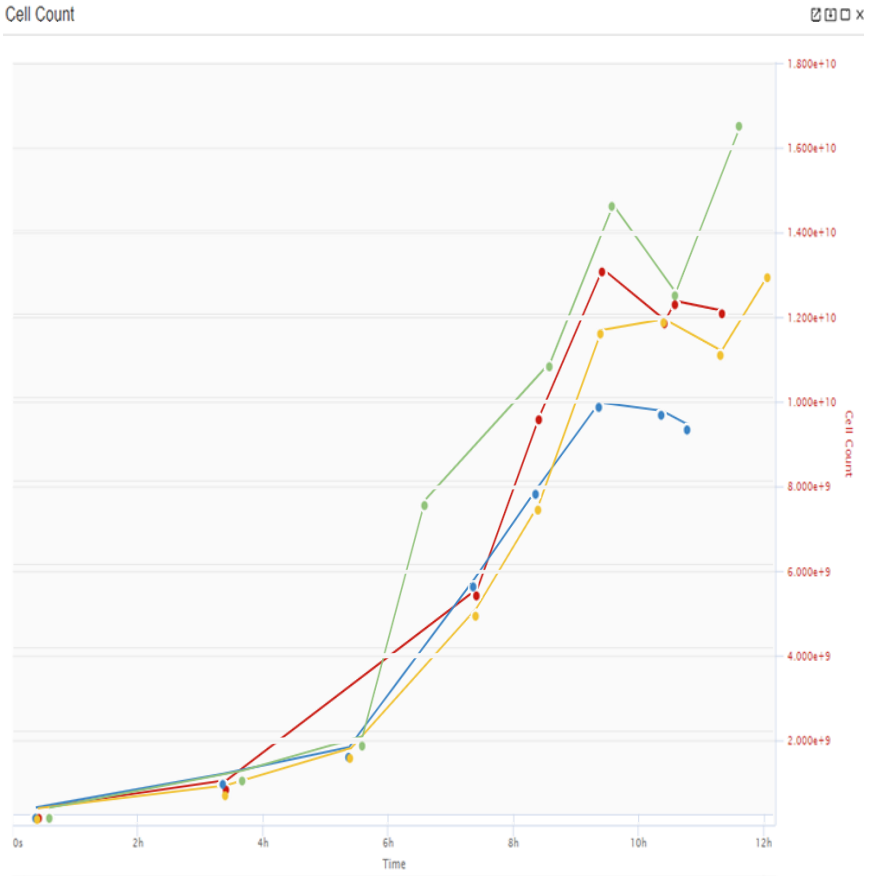
Case Study #3: High Variability in Probiotics Concentration

Client: Probiotics Industrial Producer

Problem: High variability in product concentration at the end of standard batches

Context:

- At the end of a batch (EOB), the Client starts freeze drying the bacteria to produce the probiotics
- Not being able to measure glucose in real-time, they define years ago the “End of batch” to be:
  - EOB: **when pH profile switches from decreasing to increasing**
  - Hypothesis: resulting from glucose deprivation
- Client acquired the BioIntelligence Analytics Solution™ to automatize the end of batch, with hopes to reduce variability
- Our team began helping them to implement the automation and then, we figured out something…



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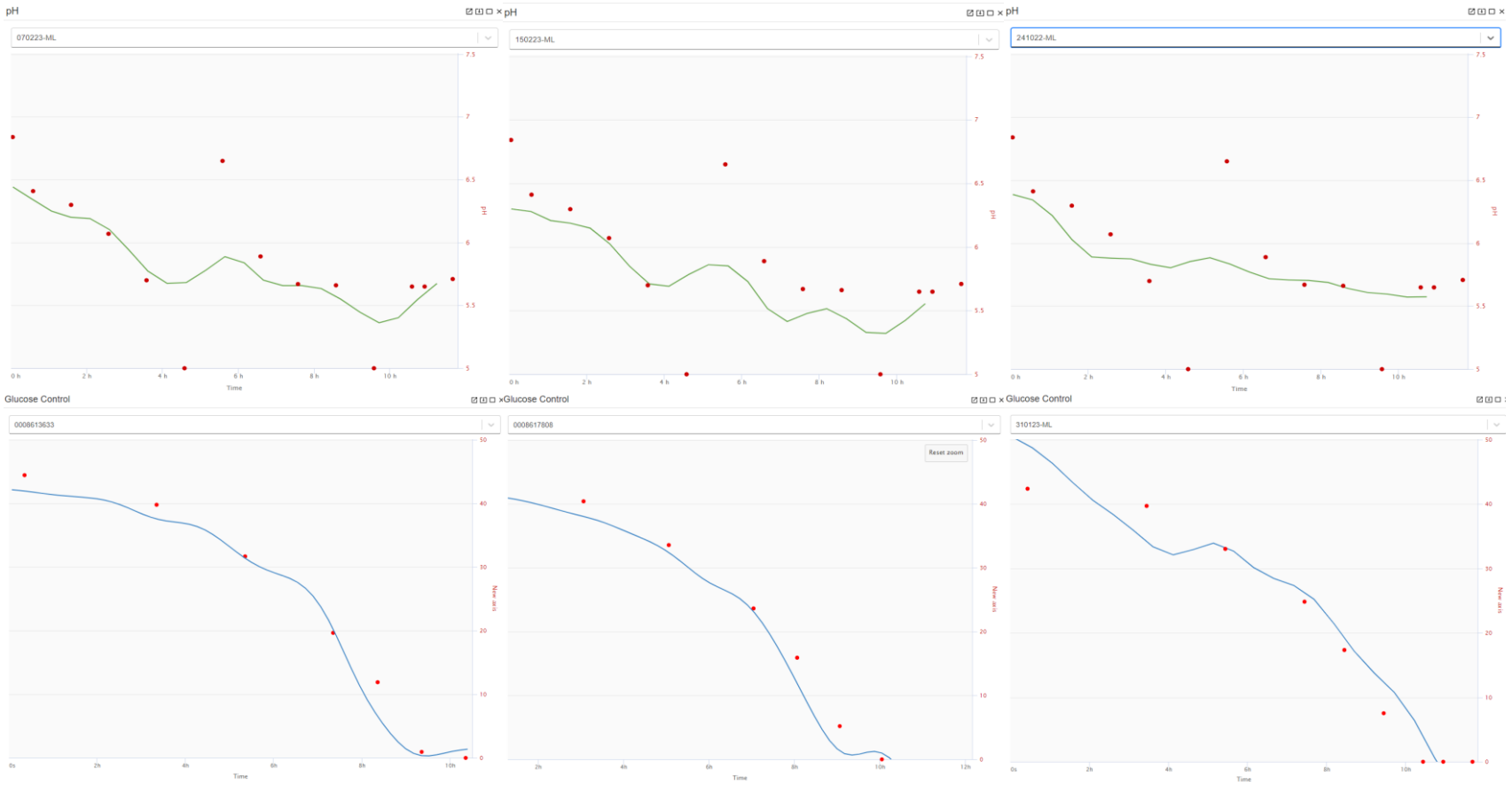
Case Study #3: High Variability in Probiotics Concentration

1. To implement EOB automation, we had to **monitor pH live** using the BAS…

pH

Glucose concentration



Accuracy and Precision to enable Automation

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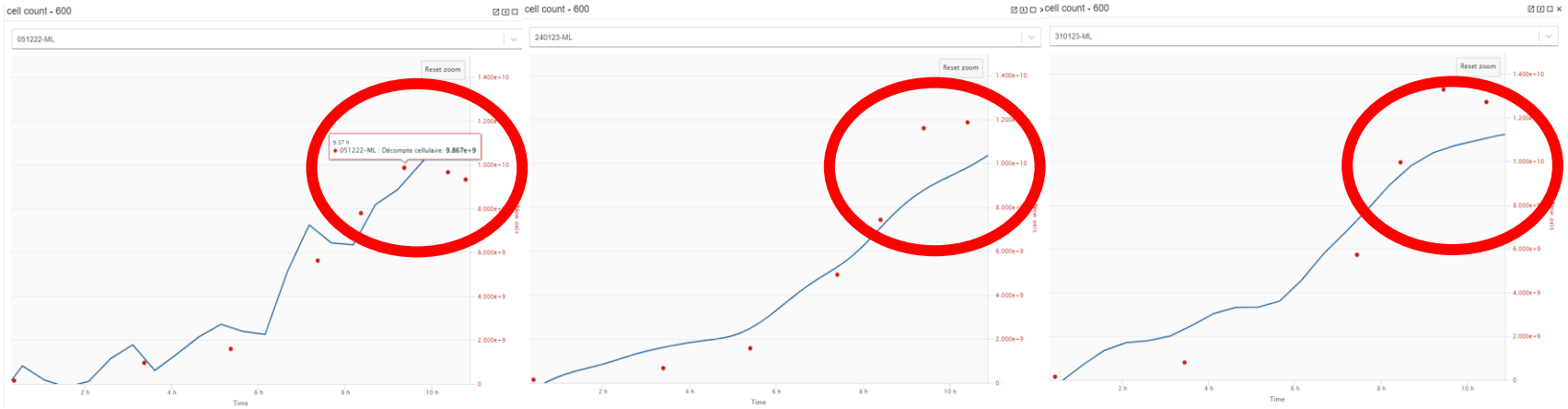
Case Study #3: High Variability in Probiotics Concentration

1. … but it was not as good with Cell concentration:

Cell concentration
(MV models)



Cell concentration
(RNN models)

(RNN did not improve significantly the results)

Accuracy problems occur close to the EOB. **Something happen then, before EOB?**

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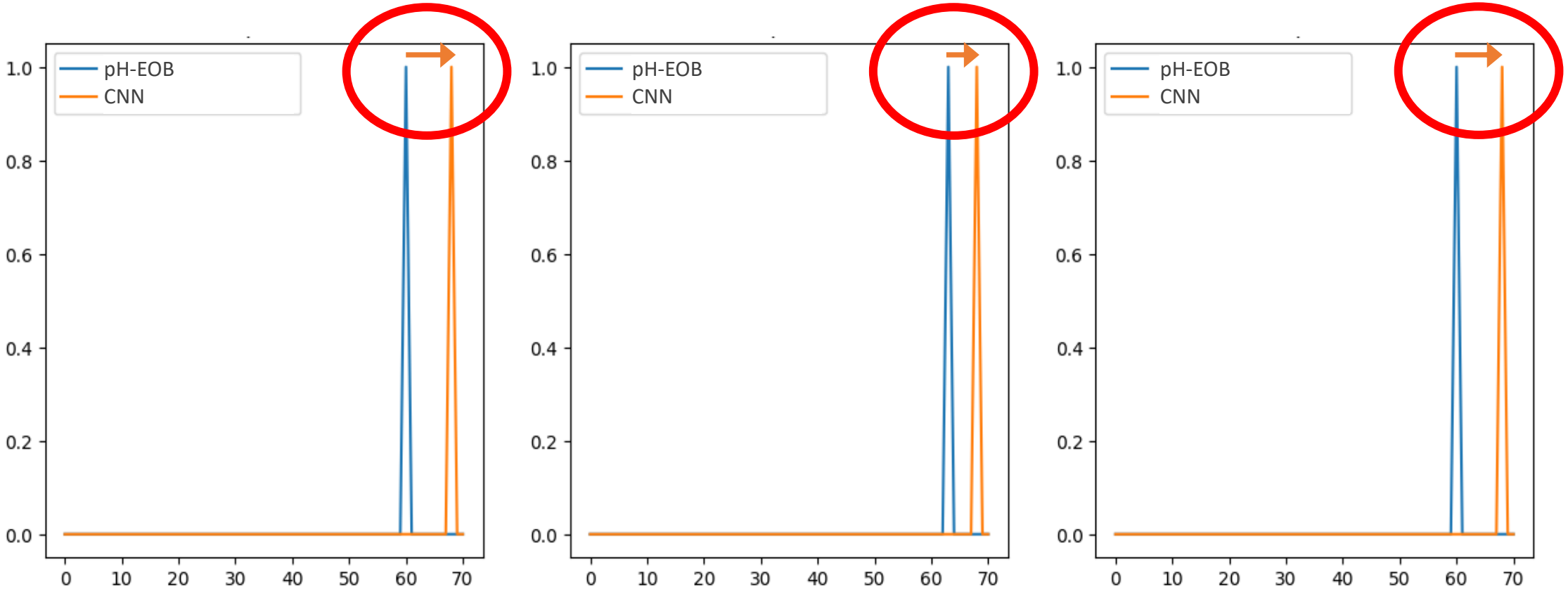
Case Study #3: High Variability in Probiotics Concentration

2. Looked for alternative solutions:
   - Can we use CNN to predict EOB (as defined from pH indication)?



EOB predicted by CNN is always 120-150 min late on pH-EOB. **CNN on pH-EOB is NOT the solution.**

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Case Study #3: High Variability in Probiotics Concentration

pH-EOB Hypothesis:

- Current use of pH-EOB does not prevent **Variability**
- Modeled pH will NOT help, since it fits offline pH
- CNN on pH-EOB does NOT work and is always late
- Cell concentration modeling indicates something happens hours before pH-EOB.
  - Metabolism → Fluorescence ≠ Cell Concentration
  - A metabolic shift happens before end of growth (from Cell concentration)
  - Problems happens before pH-EOB
  - pH is not good indicator for “End of batch” and will not enable solving the variability problem

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Case Study #3: High Variability in Probiotics Concentration

pH-EOB Hypothesis:

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  - A metabolic shift happens before end of growth (from Cell concentration)
  - Problems happens before pH-EOB
  - pH is not good indicator for "End of batch" and will not enable solving the variability problem

- **Since we have been able to model Glucose, why not using Glucose as an indicator for EOB now on?**

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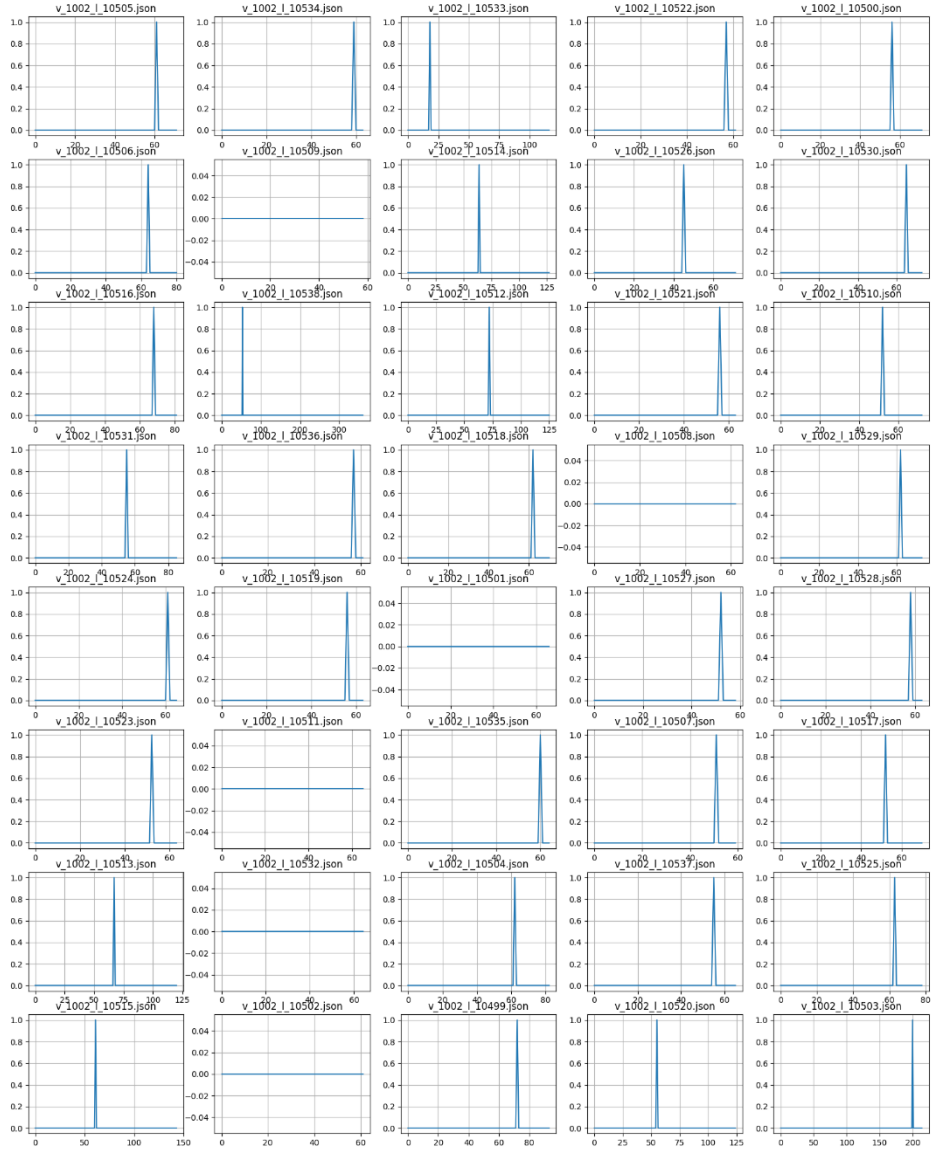
Case Study #3: High Variability in Probiotics Concentration

3. Exploring the feasibility of a “Glucose-Deprivation-Indicator” (GDI):
   - First, apply glucose model on all fermentations available to identify GDI (i.e. the moment Glucose is completely consumed)



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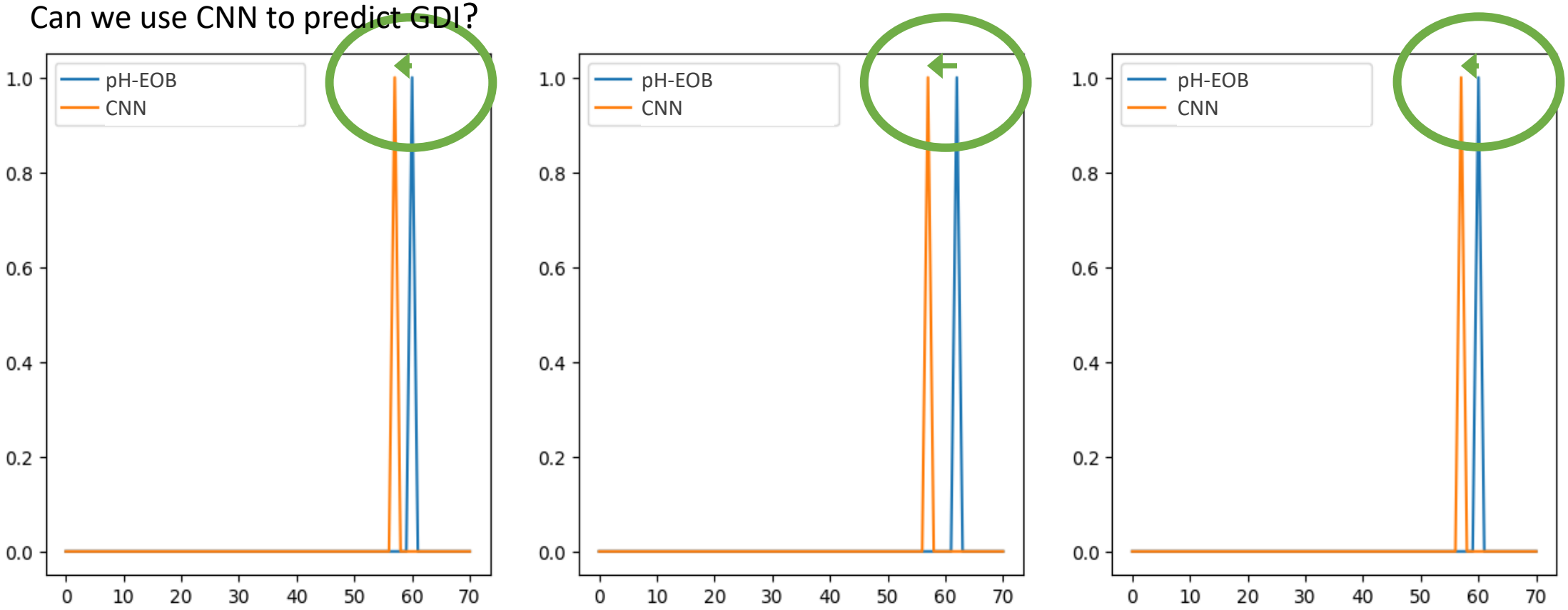
Case Study #3: High Variability in Probiotics Concentration

3. Exploring the feasibility of a “Glucose-Deprivation-Indicator” (GDI):
   - First, apply glucose model on all fermentations available to identify GDI (i.e. the moment Glucose is completely consumed)
   - Can we use CNN to predict GDI?



CNN is closer to GDI (than pH-EOB) and always 30-45 min earlier. **CNN-GDI is a lead-predictor of the actual EOB.**

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Case Study #3: High Variability in Probiotics Concentration

Glucose-Deprivation-Indicator Hypothesis:

- GDI is captured by CNN **30-45 minutes before** Glucose Deprivation
- Strong indication of GDI being an indicator of a metabolic shift leading to what should be the EOB
- **GDI is a very high-potential & actionable indicator to prevent Variability**
- Implementation is ongoing…

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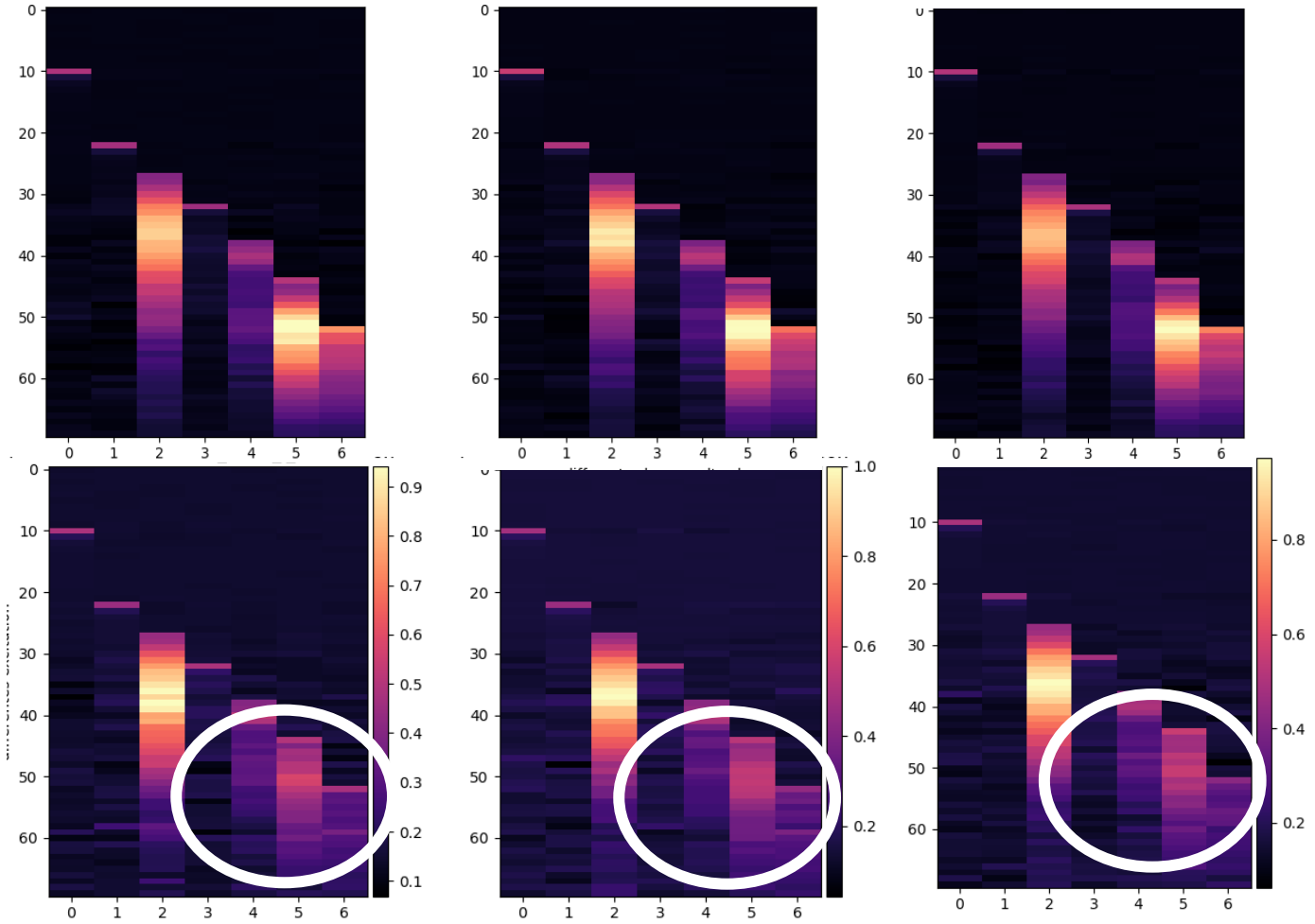
Case Study #3: High Variability in Probiotics Concentration

4. Bonus: Exploring Clustering as a Real-time indicator of Quality vs Problems
   - Comparing 3D optical spectrum: Beginning vs End of batch



3D imprints at Start and at End are different. Does clustering help identify relevant models?

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Case Study #3: High Variability in Probiotics Concentration

4. Bonus: Exploring Clustering as a Real-time indicator of Quality vs Problems
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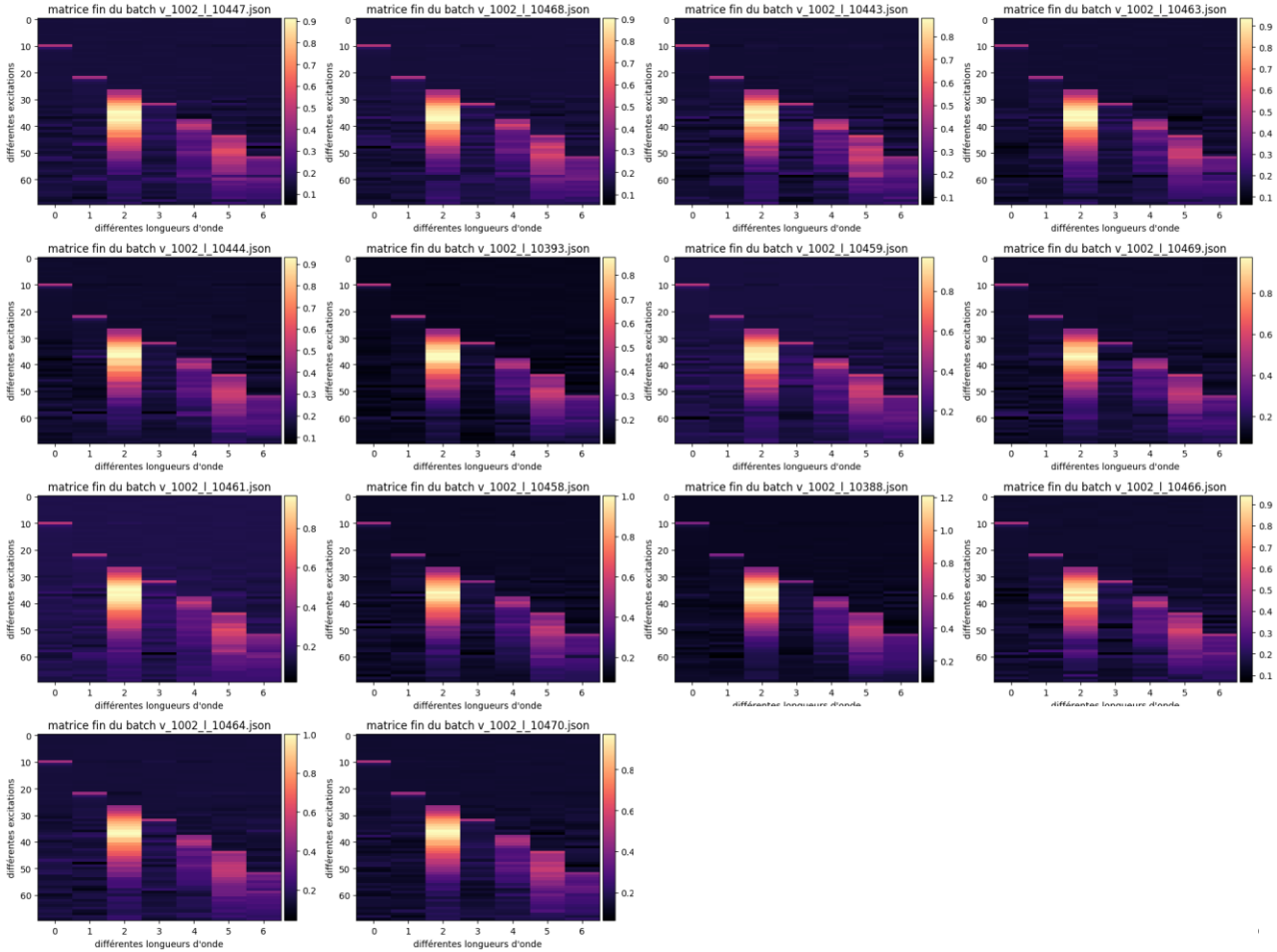

End of batch 3D imprints also contain slight differences.

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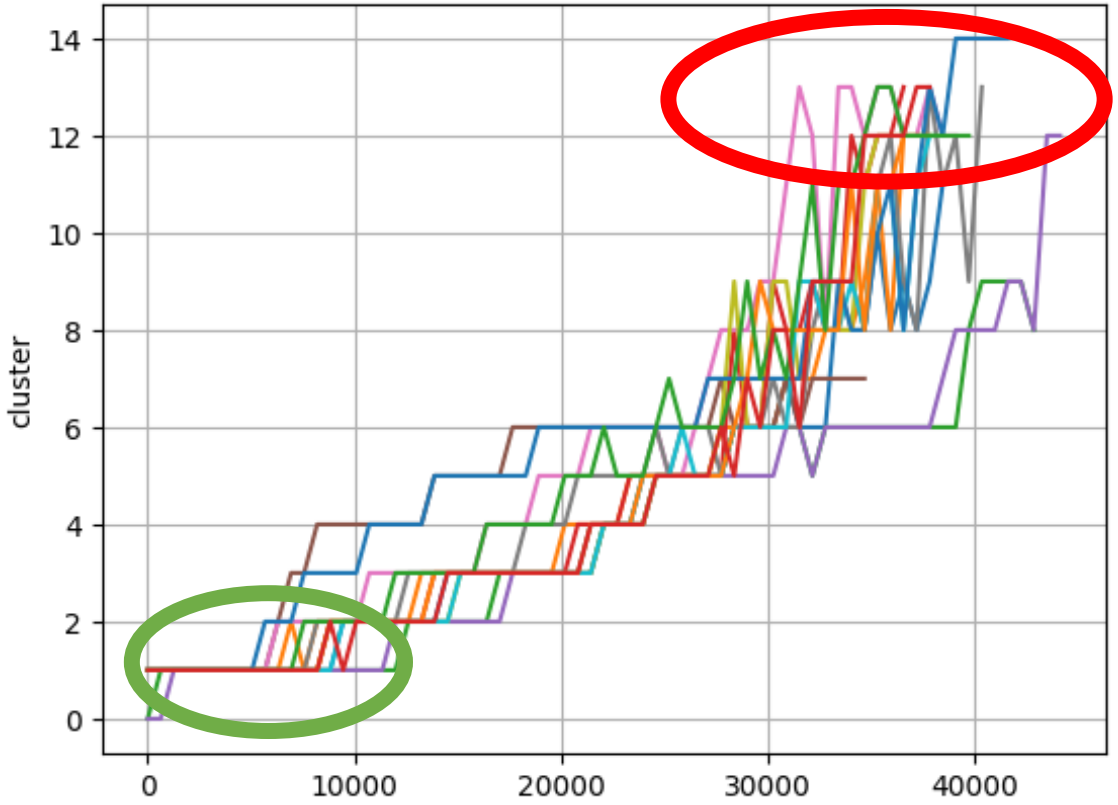
Case Study #3: High Variability in Probiotics Concentration

4. Bonus: Exploring Clustering as a Real-time indicator of Quality vs Problems
   - Using Clusters to:
     a. **Characterize the quality of fermentation right from the start**
     b. **Get notification (Try to avoid?) when GBI is to be triggered**



End of batch 3D imprints also contain slight differences.

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Case Study #3: High Variability in Probiotics Concentration

Conclusion:

- **pH-EOB Hypothesis is wrong and of no help to prevent Variability**
- **CNN-GDI revealed to be a high-potential & actionable lead-predictor for the EOB to come**
- **Clustering already enabled the team to assess Initial fermentation quality & GDI triggering**

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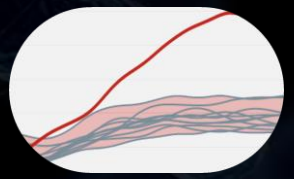
Impacts on Bioprocess Metrics

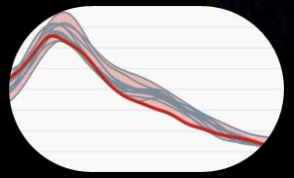


Increase Conversion Yield

+10%

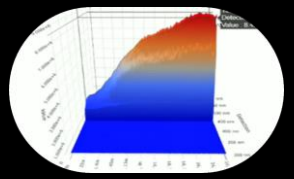
Maximize Profit

ROI 33x



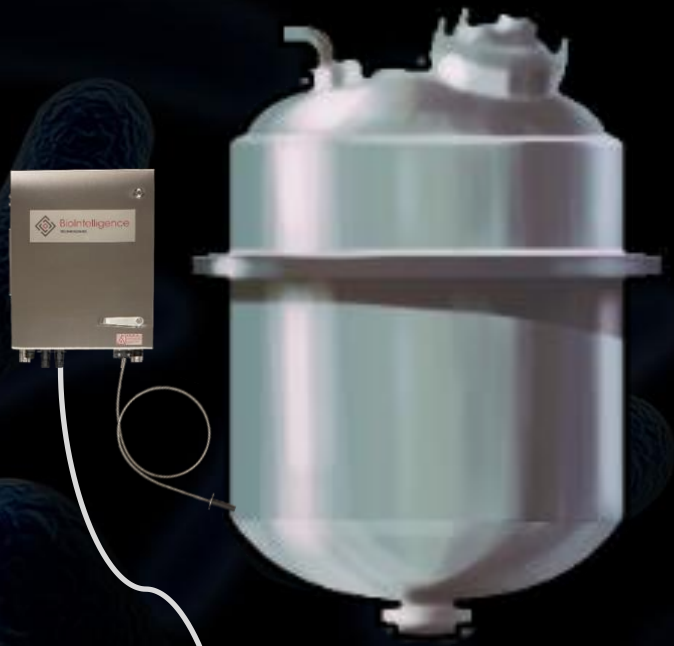
Maximize Reproducibility

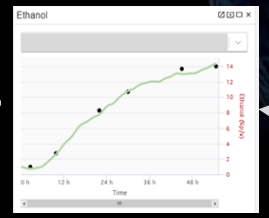
+50%

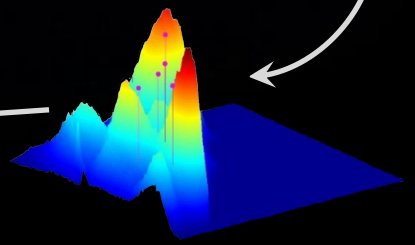


Accelerate Development

+25%







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JOEL@BIOINTELLIGENCE.COM