



Model-Based Control in Cultivated Meat Cell Cultures through Raman Spectroscopy

# Model-Based Control in Cultivated Meat Cell Cultures through Raman Spectroscopy

**Akhil Jalan (Institute for Foundations of Machine Learning, UT Austin)  
and Kai Hoeffner (Sanofi)**



*IFPAC Global 2024*

# Outline

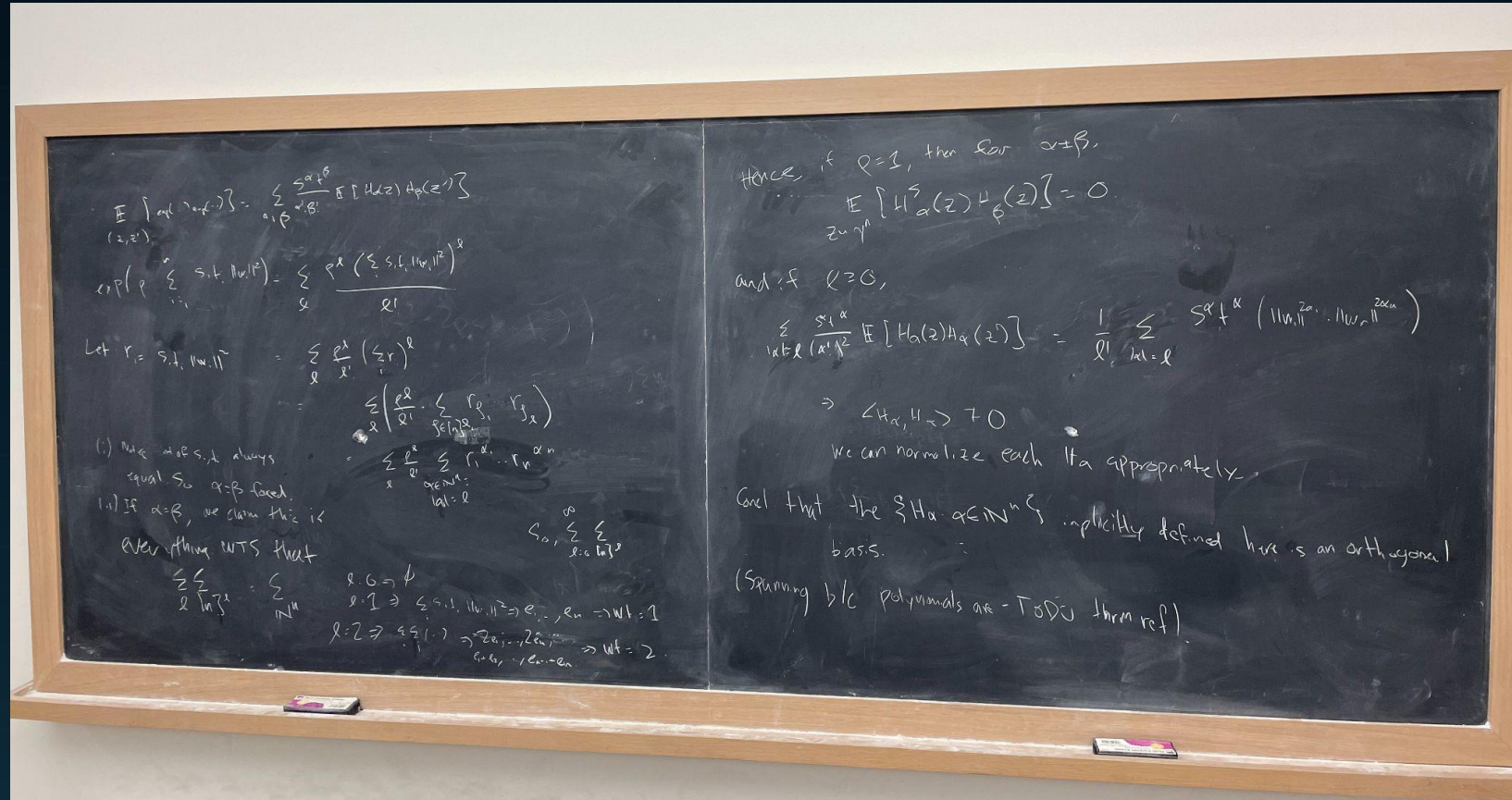
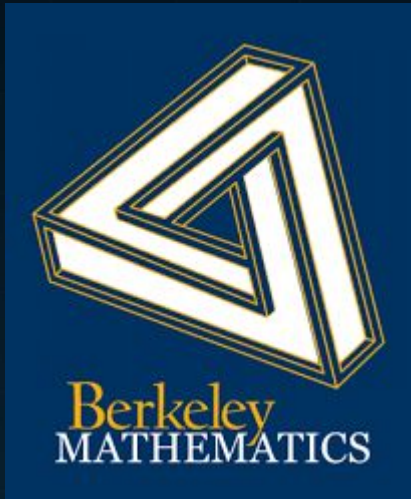
1. Background
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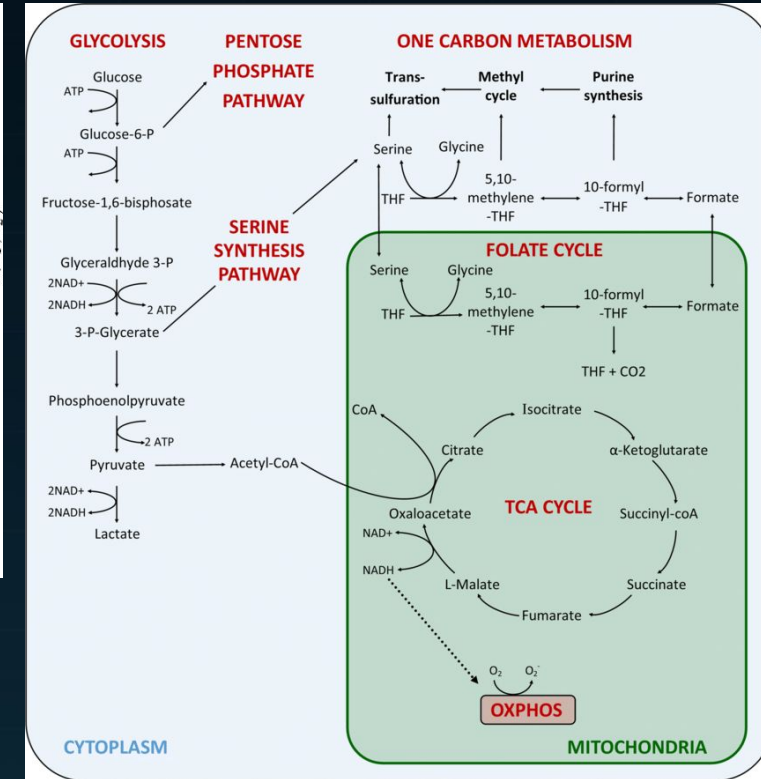
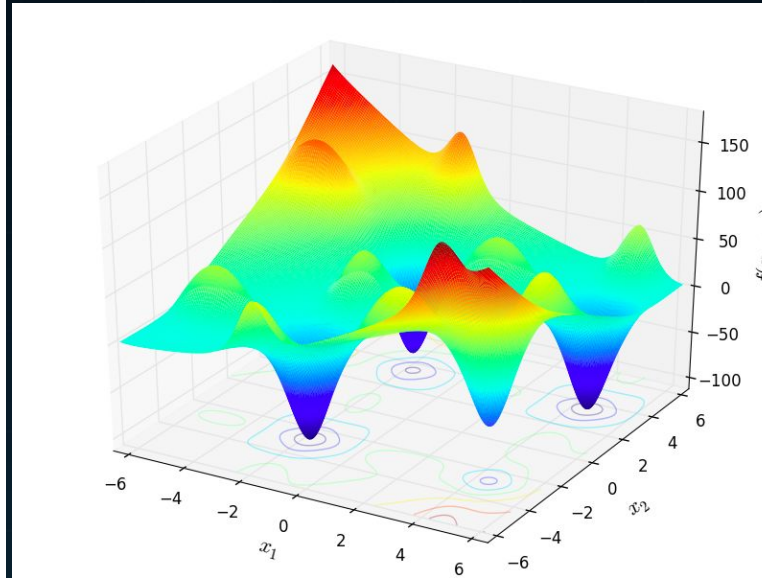
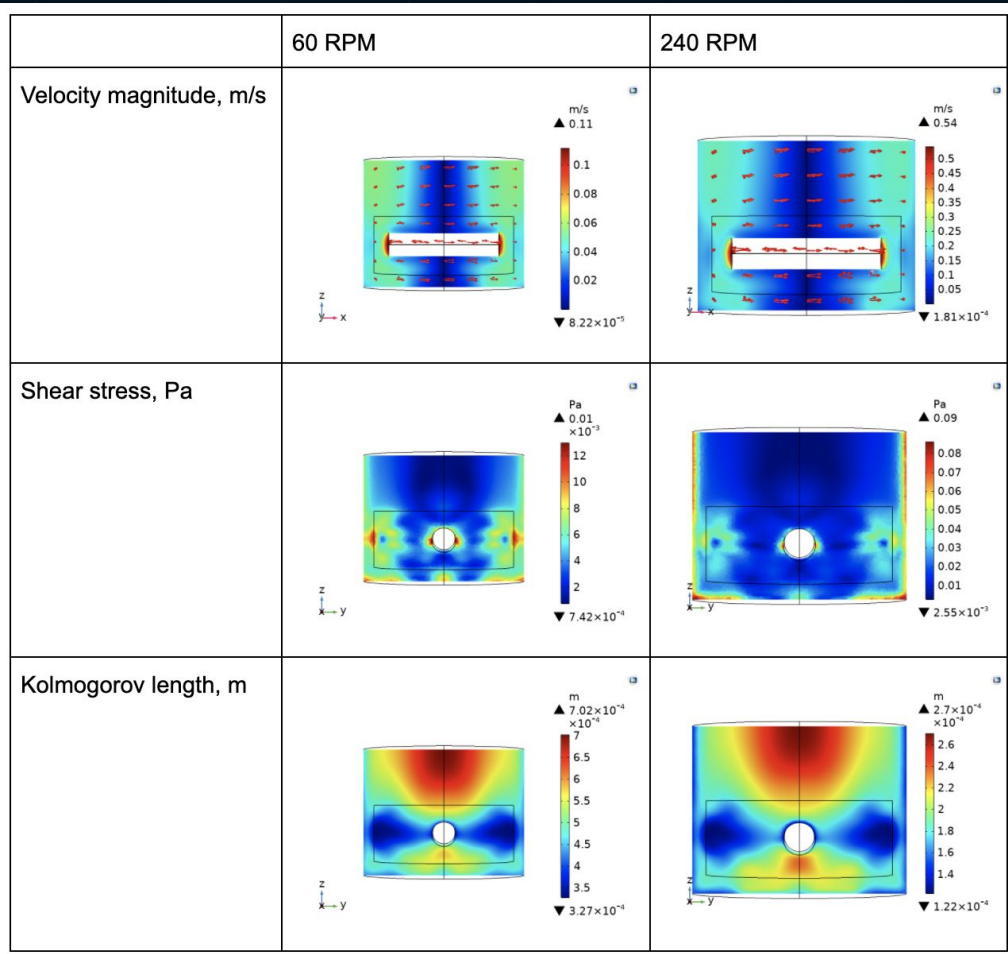
# Background



# Who Am I?



# Statistics & Machine Learning Meets Biology



<https://akhiljalan.github.io/survey-sep1.html>



What is Ark?

Enabling **cultivated meat**  
to **scale exponentially**  
through  
next-generation  
**infrastructure**



# Motivation





**ACS Publications**  
Most Trusted. Most Cited. Most Read.

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**VIEWPOINT**

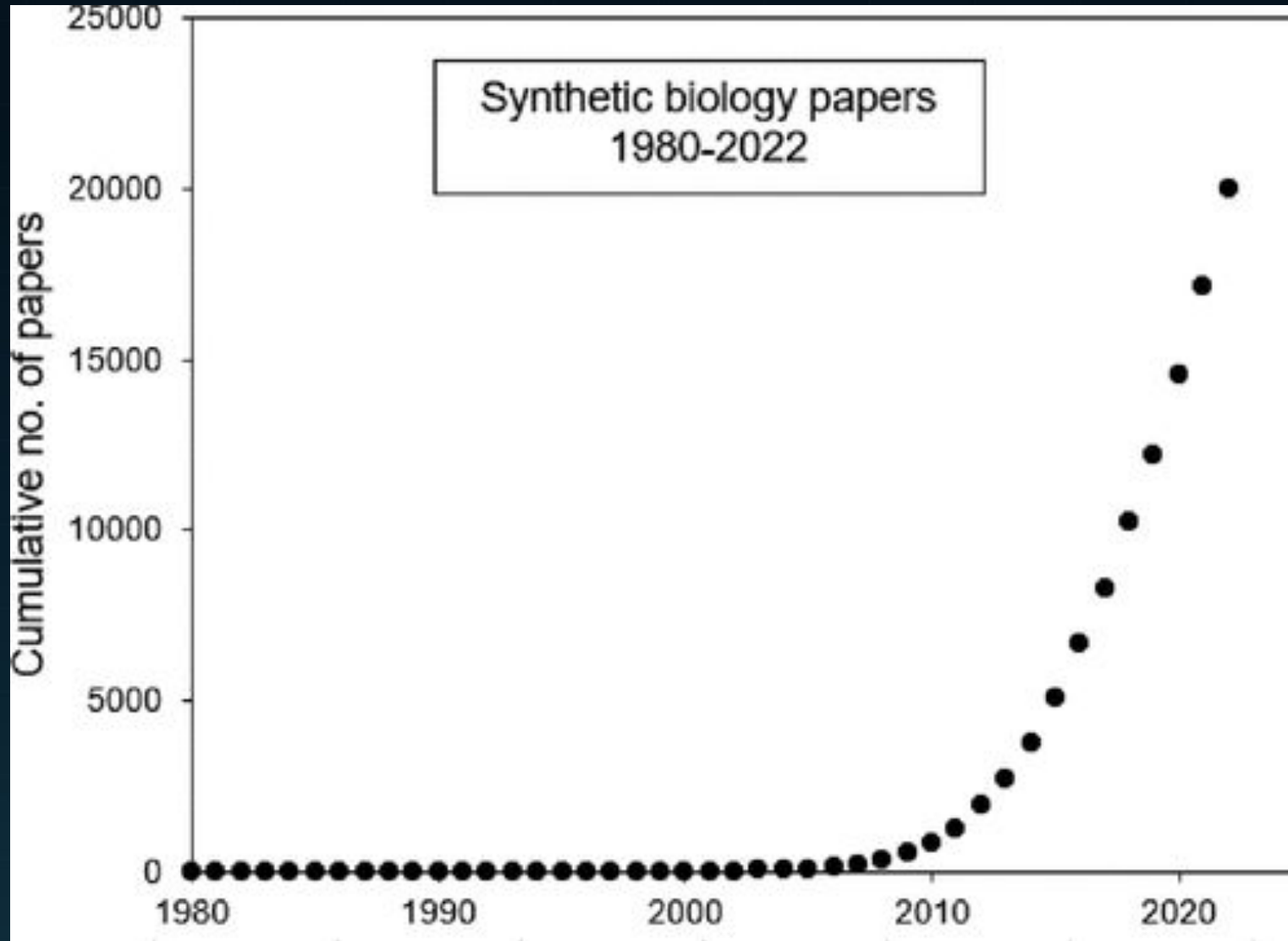
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# **Synthetic Biology—High Time to Deliver?**

Andrew D. Hanson\* and Víctor de Lorenzo\*







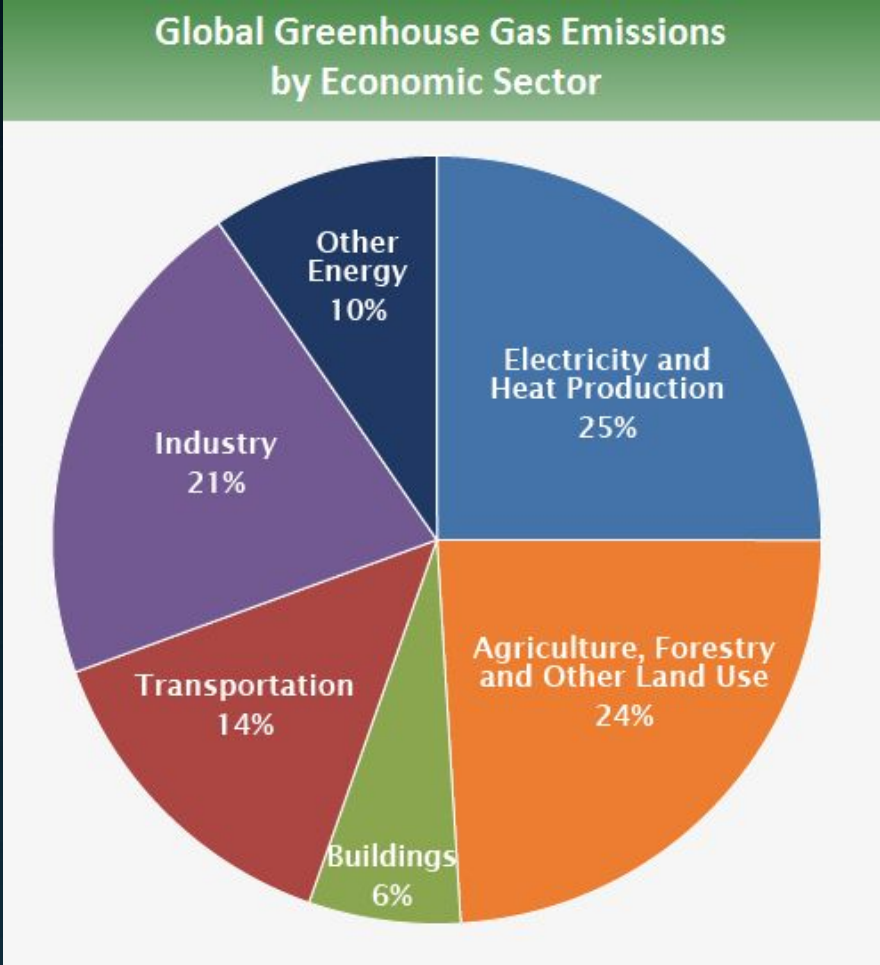
## Why Scale?

*“A habitual disregard of what is involved in scale-up is an **Achilles’ heel of the whole field...***

*Alas, the conceptual excitement occasioned by SynBio has thus far been more supported than **scale-up technologies—unfairly considered a lower-rank endeavor.”***



# Why Cultivated Meat?



Source: EPA  
<https://www.epa.gov/ghgemissions/global-greenhouse-gas-emissions-data>



# Ark Factory Concept



# **Technical Goal:** Bioprocess Optimization at Scale

## **Business impact:**

- 1. Unit Economics:** Greater yield (viable cell density) per unit of media
- 2. Capital Expenditures:** Lower doubling times → fewer bioreactors needed
- 3. Process Failure Costs:** Lower contamination risks via automation



## World Economic Forum Agrees

***“The limiting factor is the difficulty of converting laboratory-scale operations into economically viable, industrially-sized equivalents...***

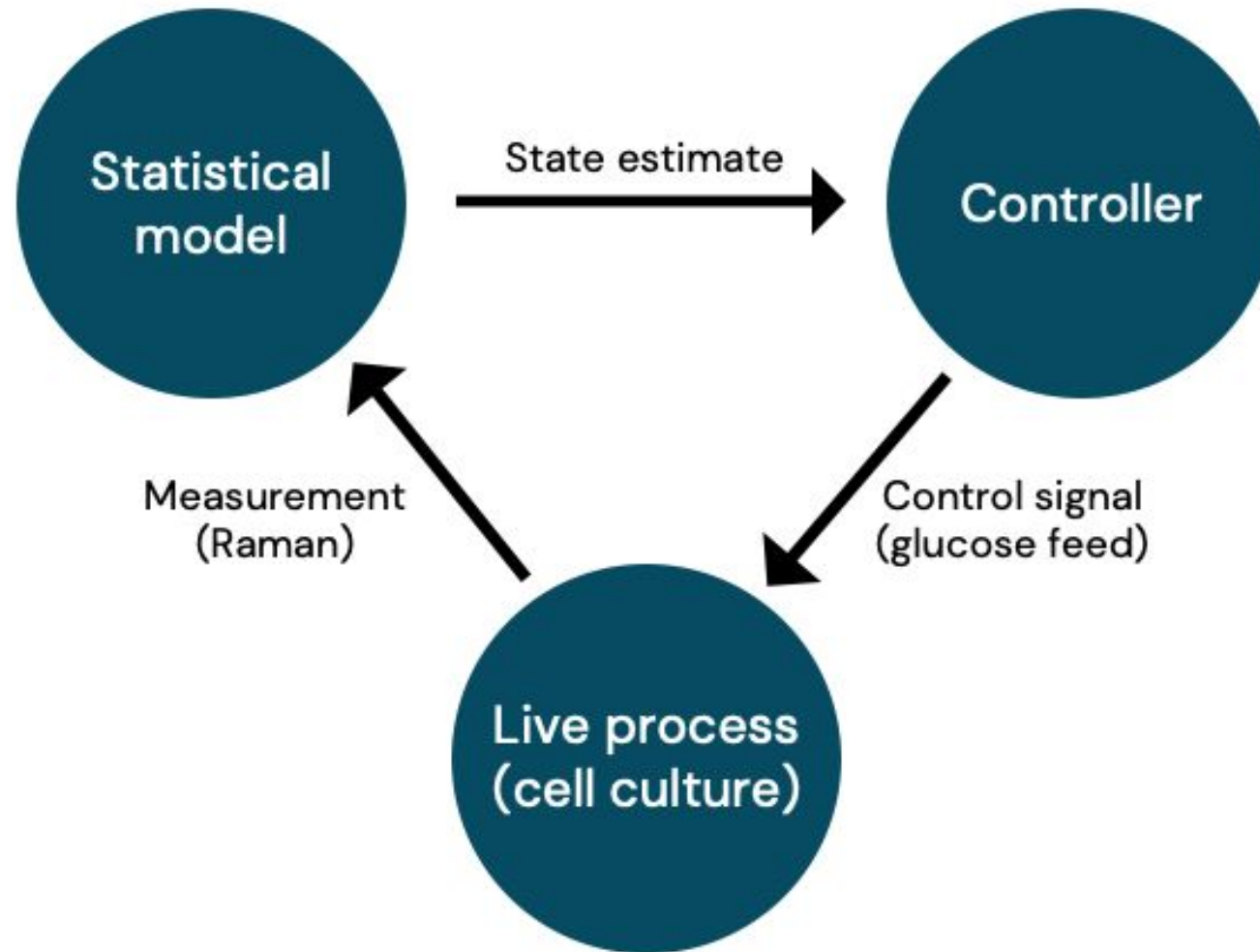
***This is not just a technical problem, but a fundamental scientific question that needs to be addressed.”***

World Economic Forum, “How Biotechnology is Evolving in the Fourth Industrial Revolution,” May 2018,  
<https://www.weforum.org/agenda/2018/05/biotechnology-evolve-fourth-industrial-revolution/>



# Our Approach

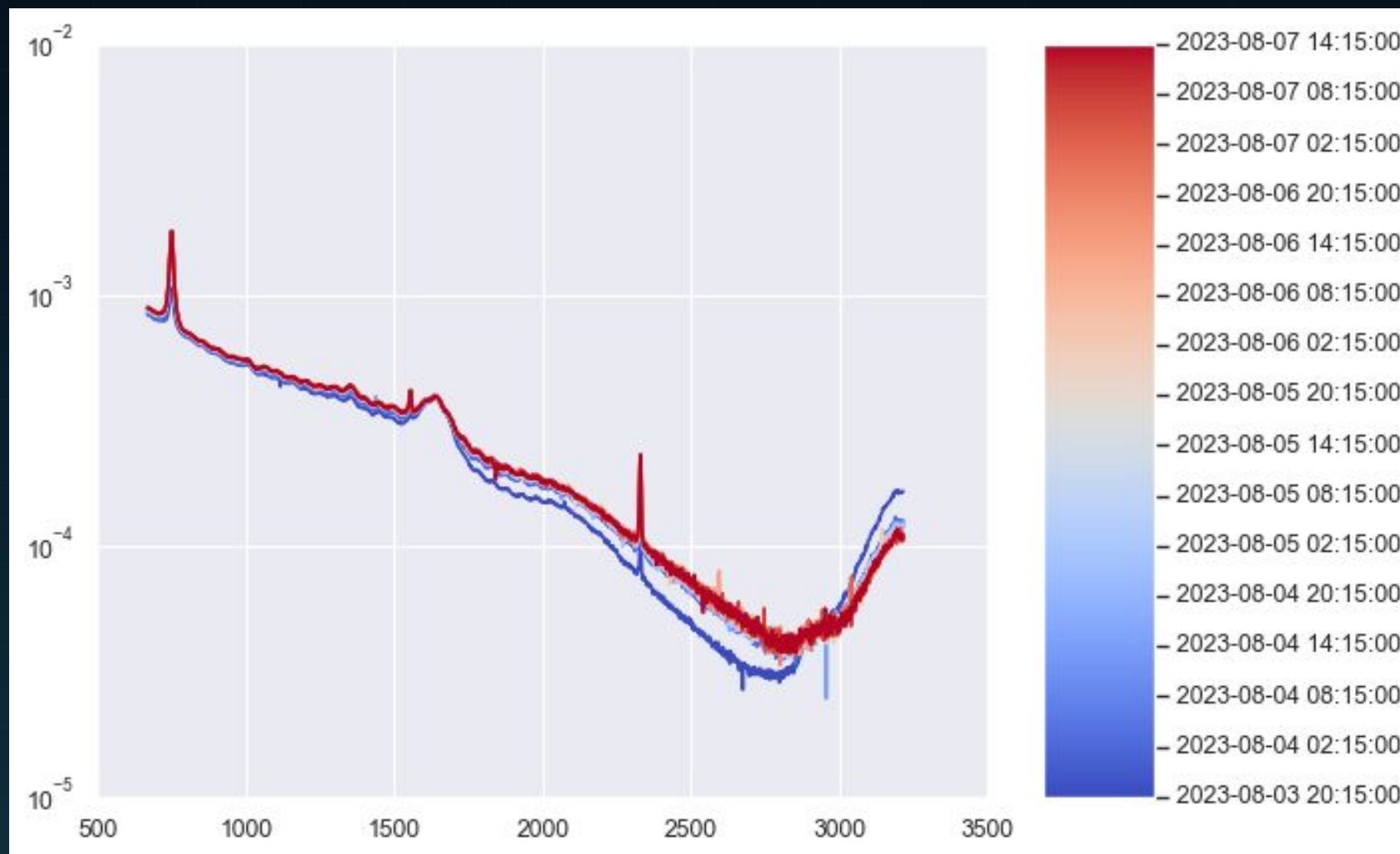




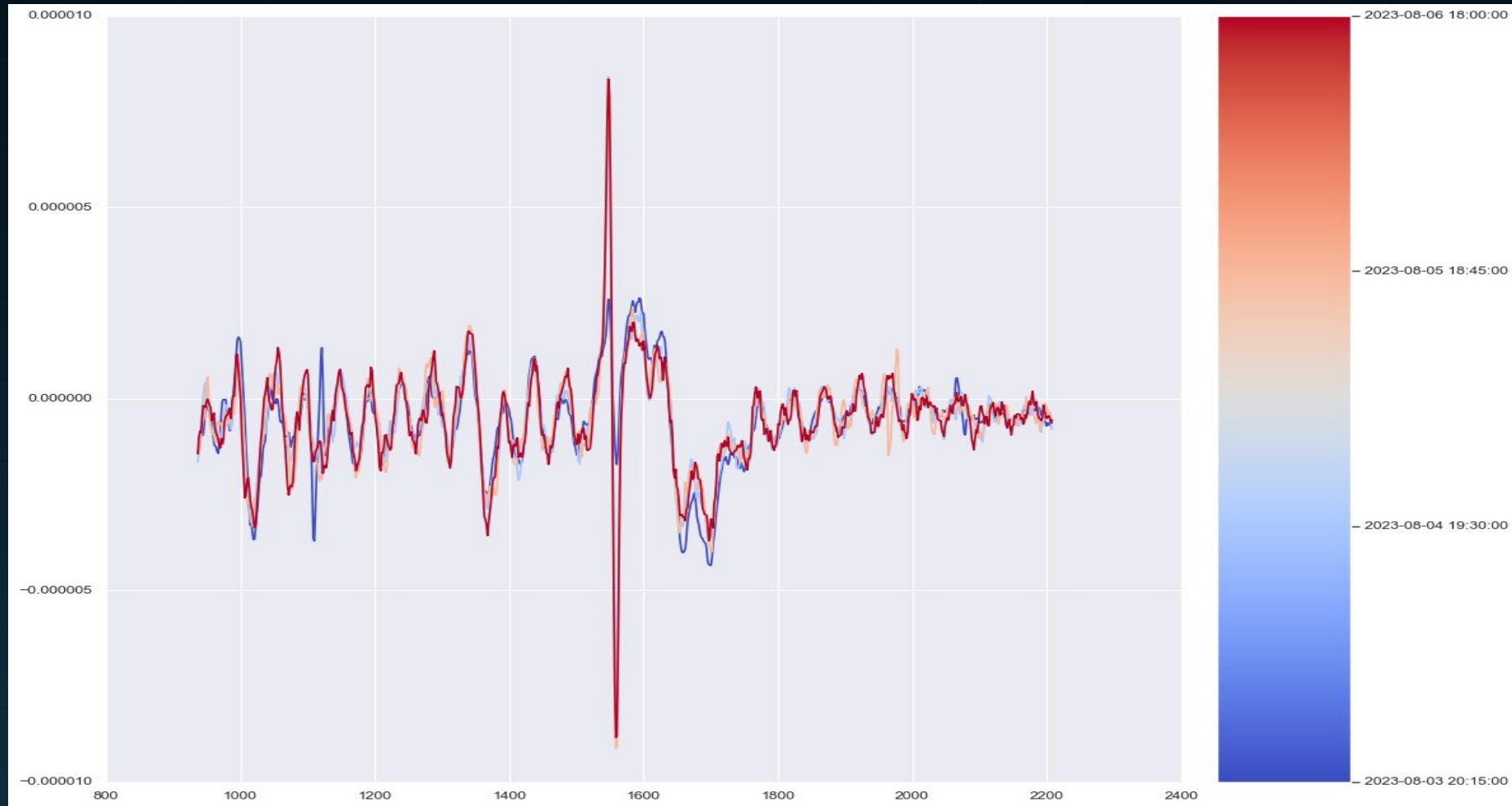




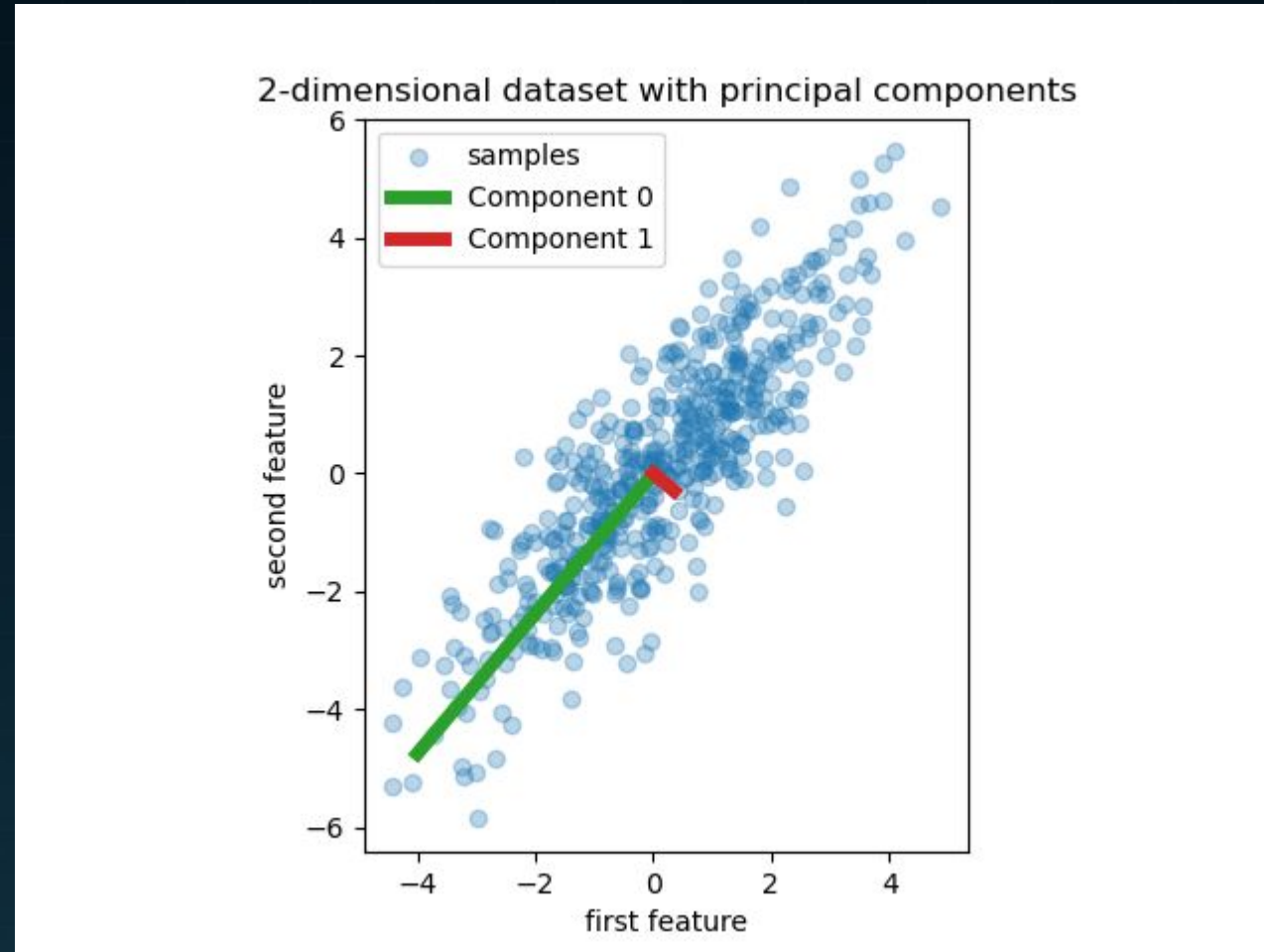
# 1) Raw Spectra



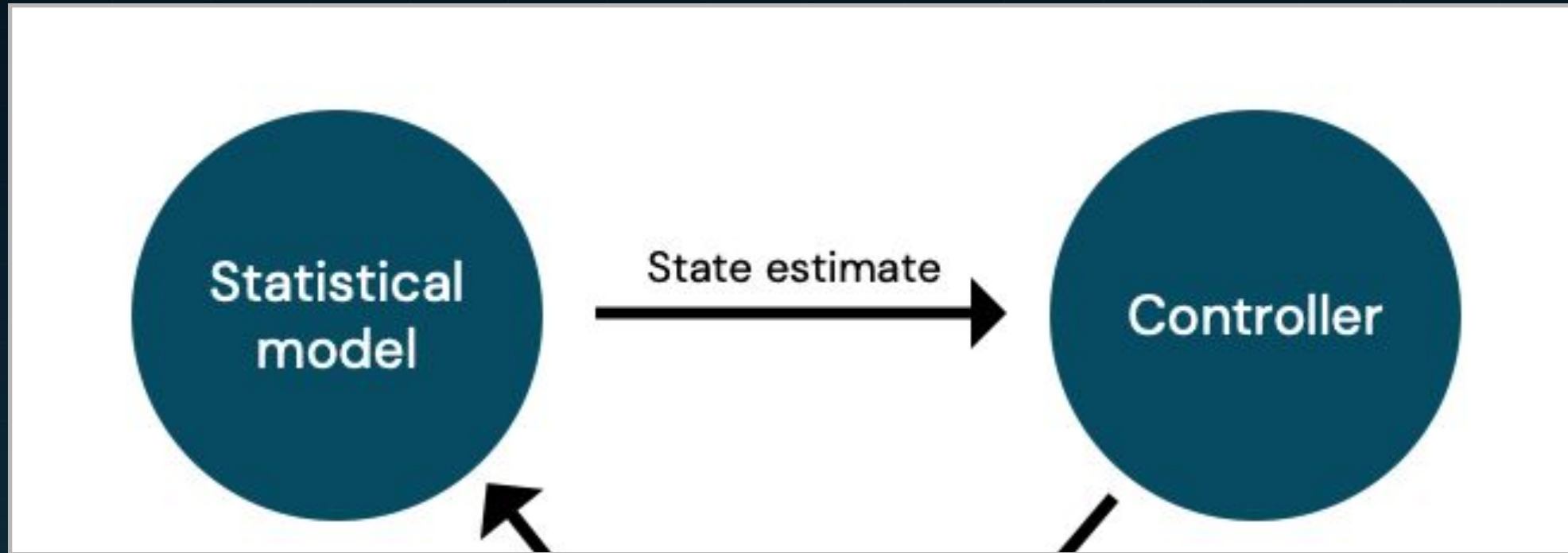
## 2) Savitzky-Golay Filtered (“Peak Enhancement”)



### 3) Multivariate Regression Model (schematic)



## 4) Moving Median Filter



# Technical Discussion

1. Fit-for-purpose loss function (NOT least squares)
  - a. Overestimation worse than underestimation
  - b. Not usually a feature in SIMCA, Eigenvector, ...



# Technical Discussion

2. Oversampling of informative runs
  - a. Because of mixed datasets
  - b. BENCHTOP, in-line
  - c. Different dates, media compositions



# Technical Discussion

## 3. Separation of variables – separate models for each target variable

- a. For PLS, you could do it all in one shot (if data were good)
- b. Different hyperparameters for lactate vs ammonia vs glucose, etc



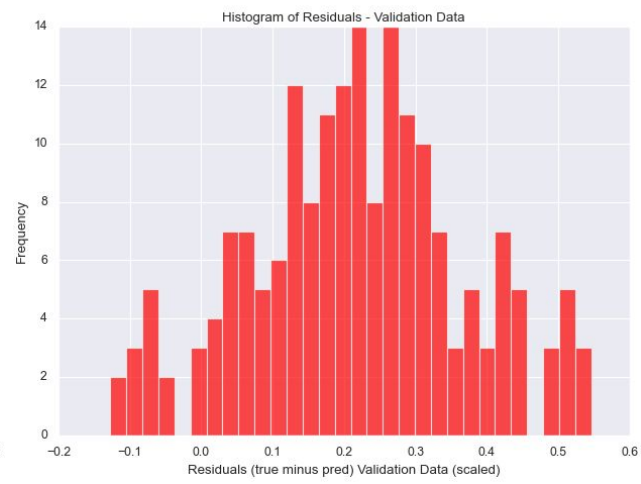
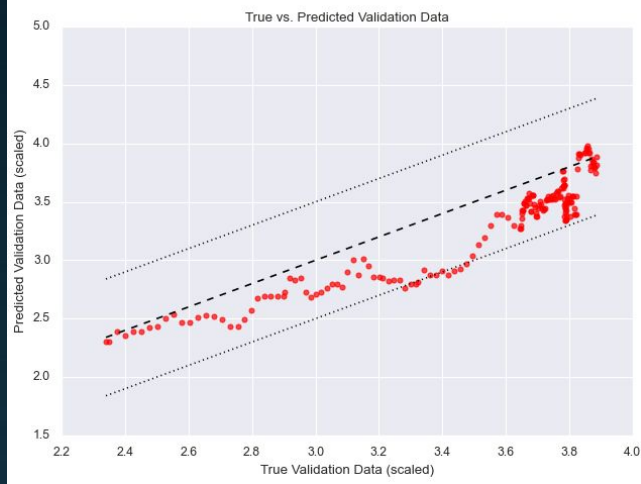
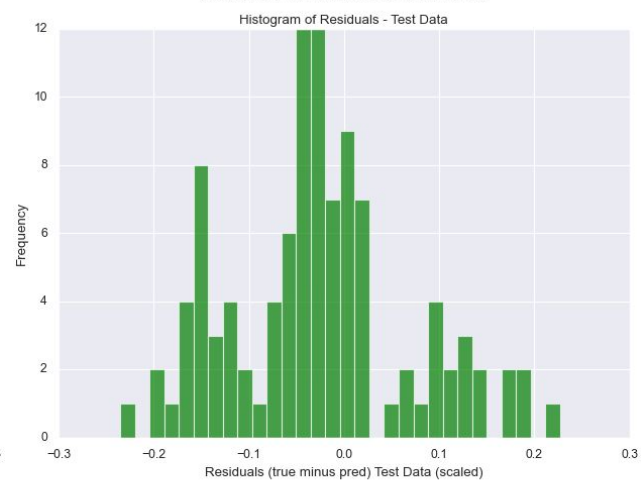
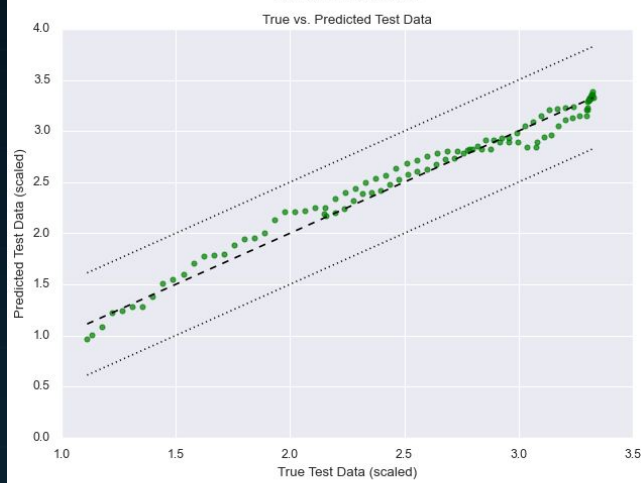
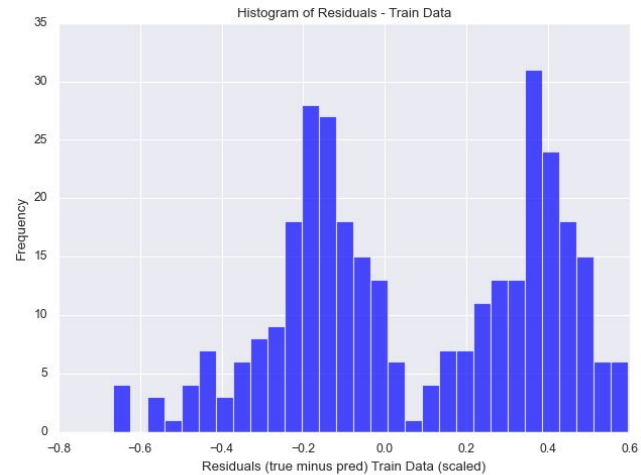
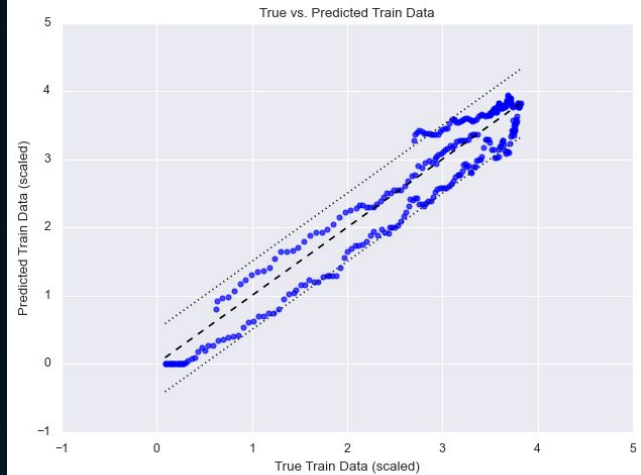


# Technical Discussion

4. Hyperparameter optimization for:
  - a. Raman filter (polynomial degree, derivative, window...)
  - b. Kalman filter (median window)
  - c. For 10+ hyperparameters, can't do grid search
  - d.



# Example Performance: Glucose Prediction



# Experimental Results



# Two Key Applications

## 1. Performance Improvement

- a. Measure via yield & doubling time
- b. Faster response to culture conditions
- c. Real-time control, not manual spiking every 24 hrs

## 2. Eliminating Manual Sampling in Decision-Making

- a. Make real-time decisions based on Raman
- b. Lower contamination risk
- c. Reusable Raman probe cheaper than one-off assays



# Experiment 1: Feedback Glucose Control

**Setup:** DF-1 cell culture in lab-scale bioreactor.

**Baseline:** No glucose control, all else held constant

## **Our Algorithm:**

Inline Raman probe

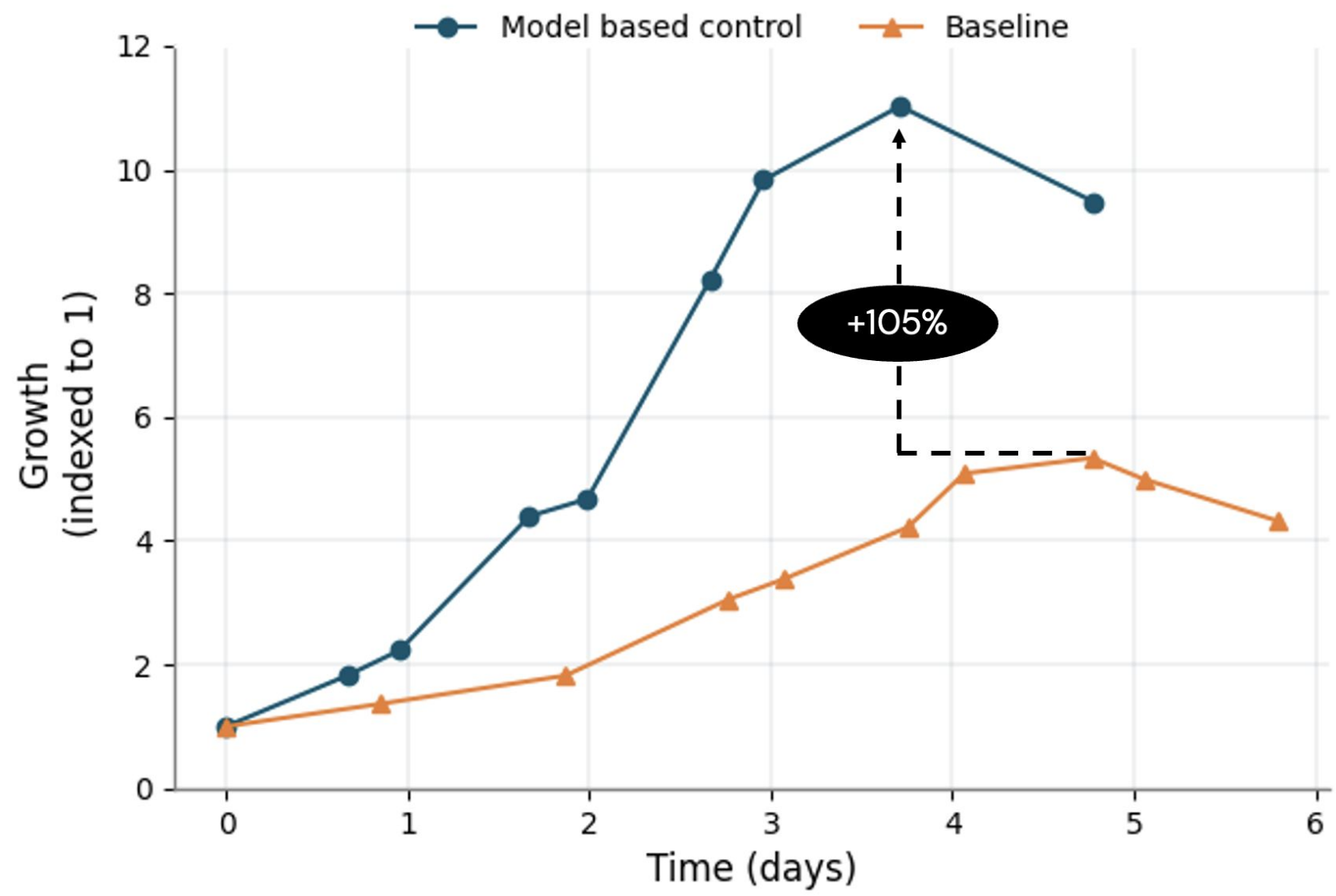
→ state estimate for glucose

→ PID Controller for glucose feed

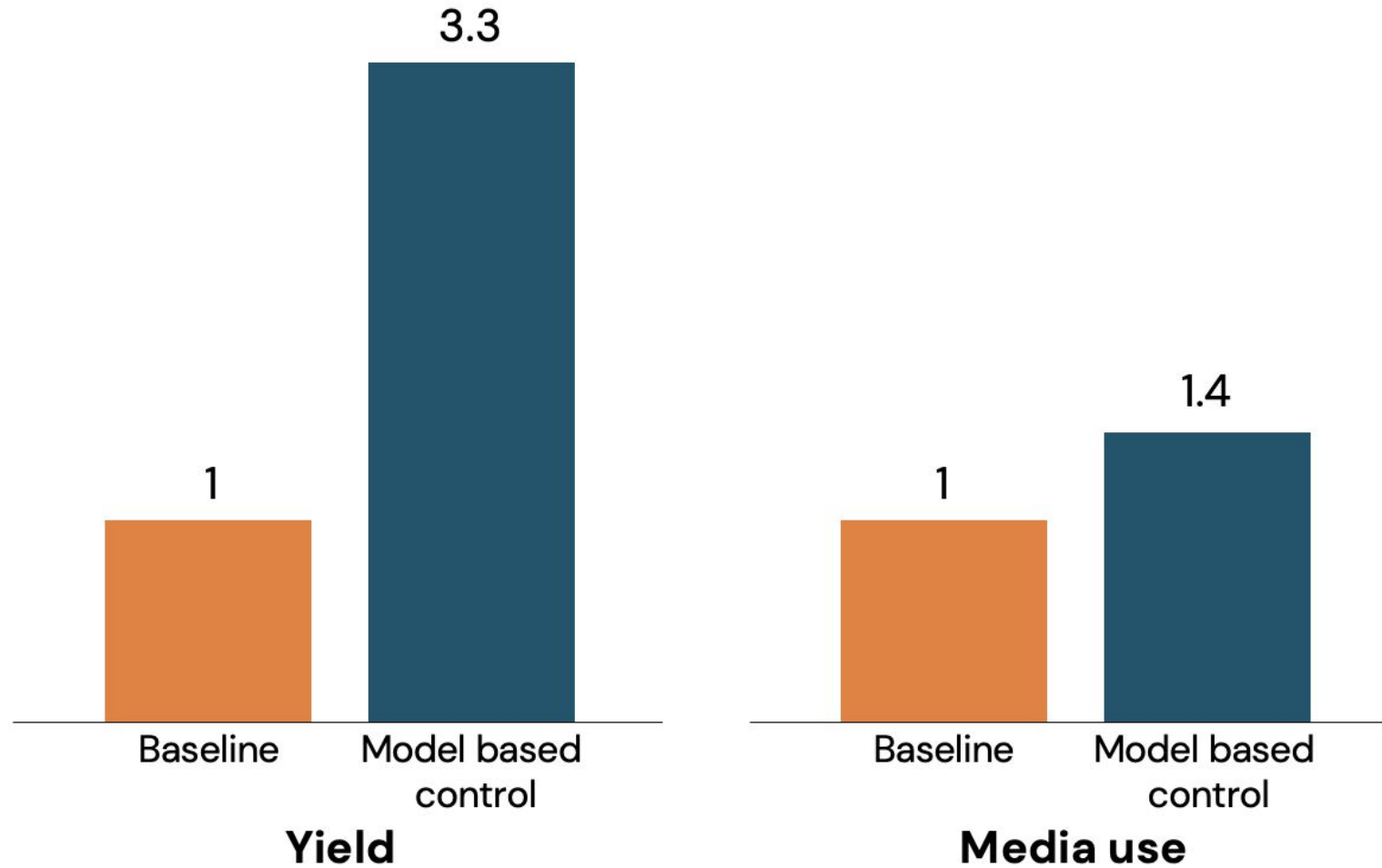
- Add glucose solution every hour
- Consistent g/L target throughout the run



# Viable Cell Density



## Annualized impact of model base control improvement over baseline (baseline indexed to 1)



# Experiment 2: “Lights out run”

**Goal:** Run a repeated fed-batch culture (partial harvest mode) where decision-making never uses offline samples

**Experiment:**

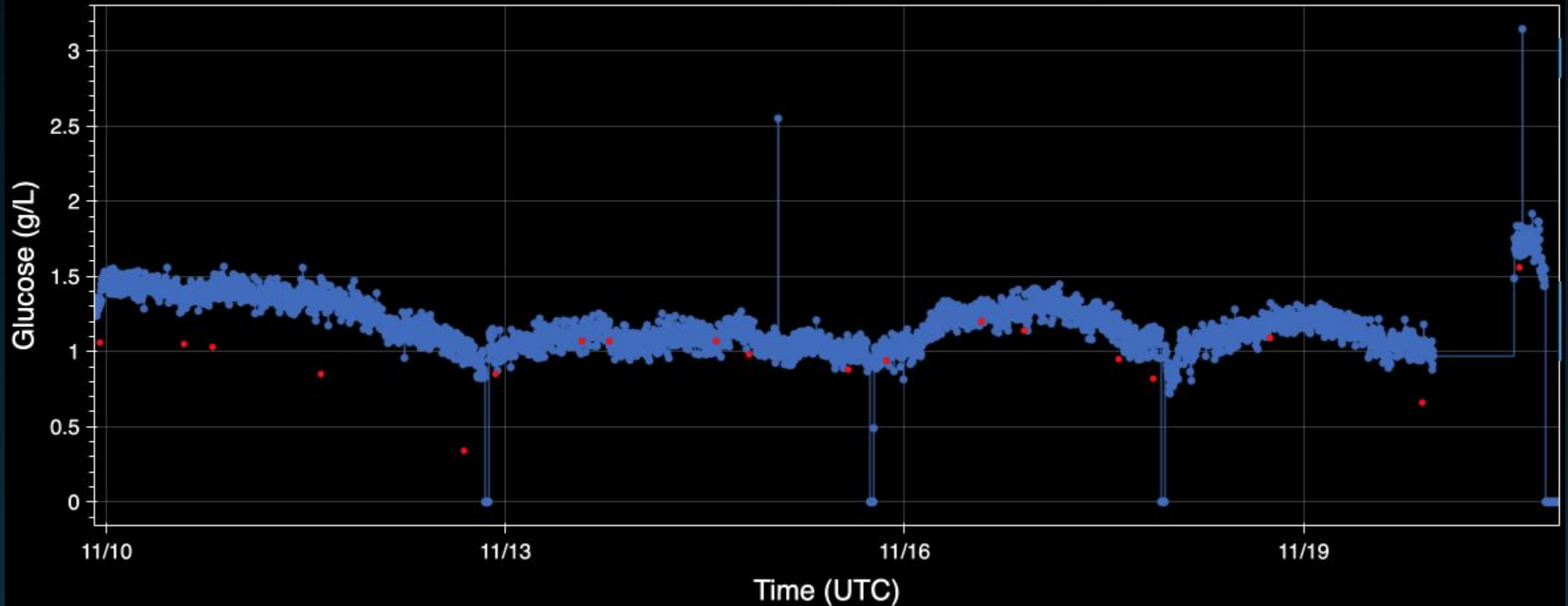
- 11-day run
- 3 partial harvests
- 19 offline samples (for post hoc assessment)





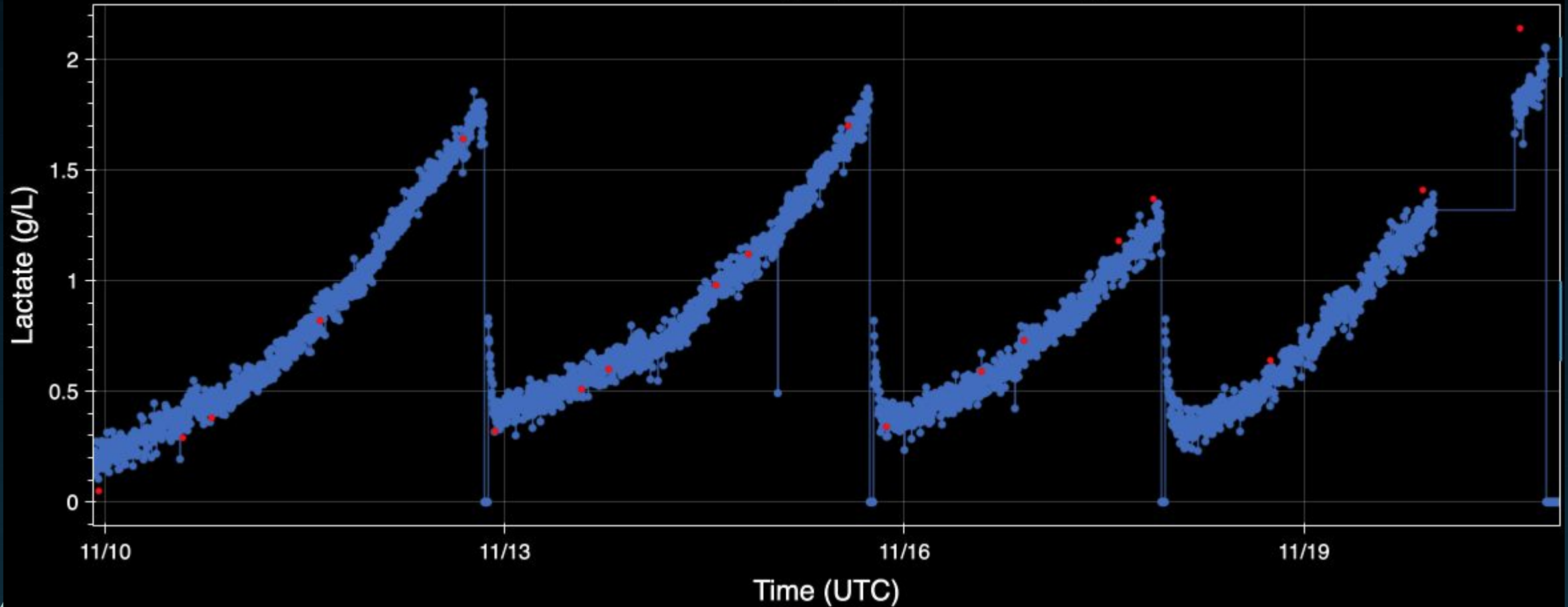
# Glucose Results

RMS Error: 0.29 g/L, expected 0.22 g/L



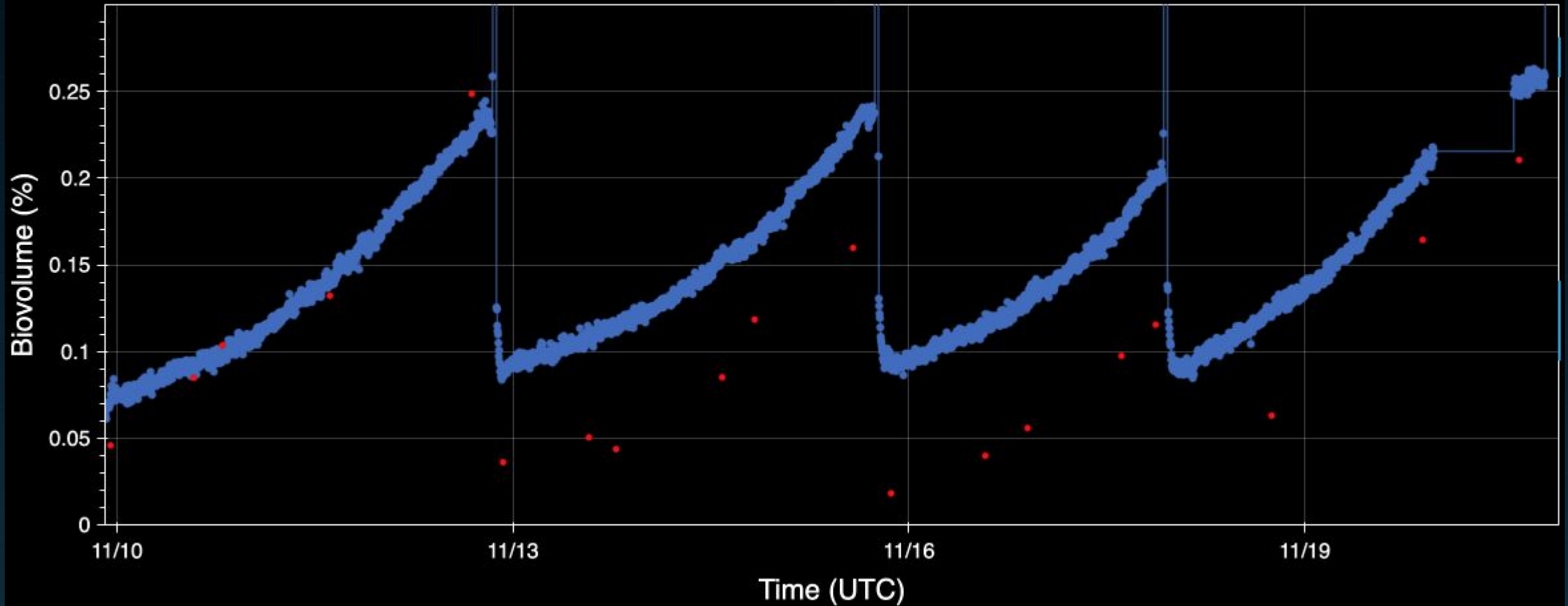
# Lactate Results

RMS Error: 0.13 g/L, expected 0.17 g/L



# Biovolume Results

RMS Error: 0.057%, expected 0.045%



# Discussion & Broader Impacts

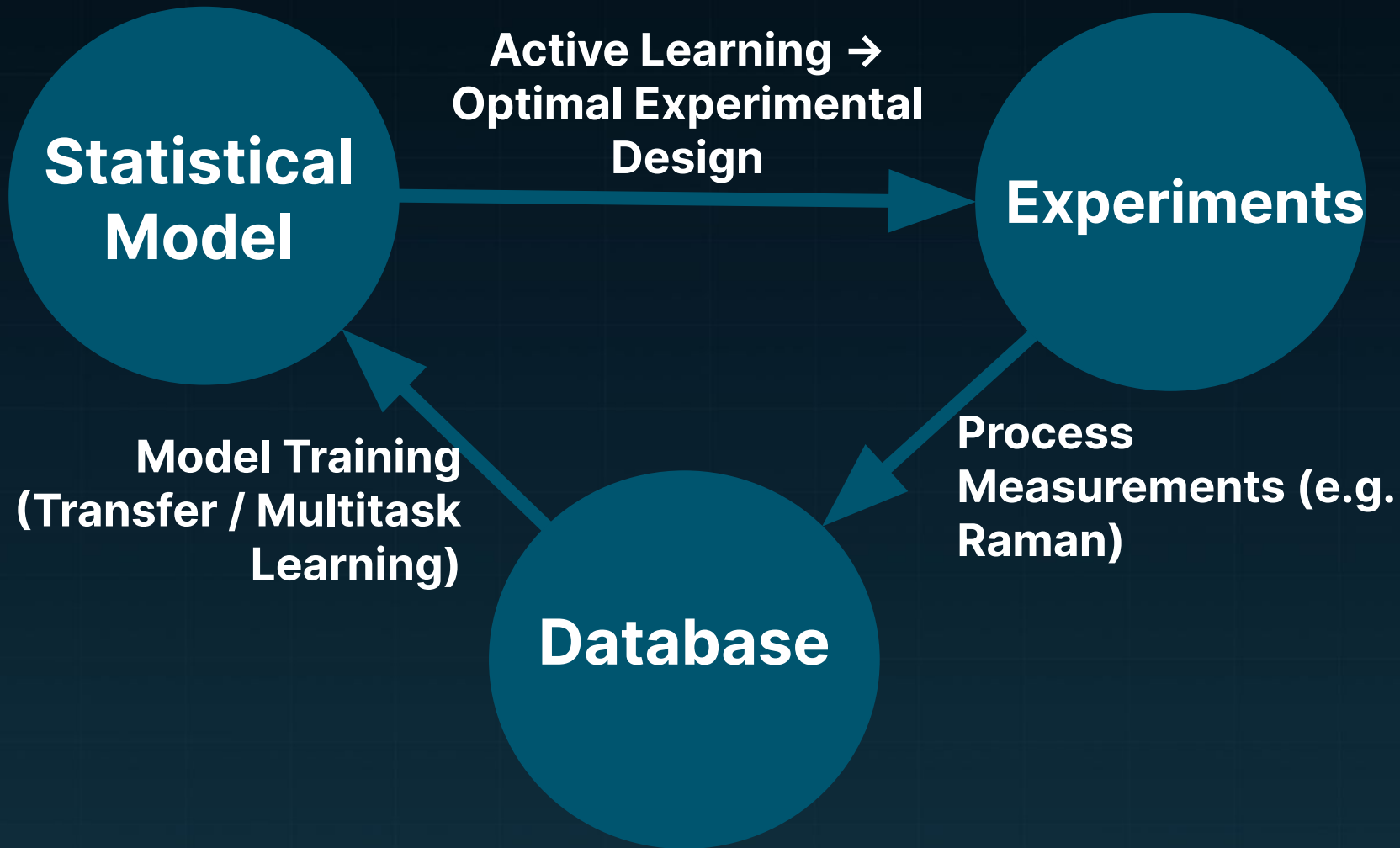


# Discussion & Future Directions

- Impact of **catabolic control** for cell culture (*Glacken 1988*)
  - Raman is a key tool for feedback catalytic control (*Matthews et al. 2016*)
- Inline sensing + statistical models can outperform mechanistic models such as Metabolic Flux Analysis, Monod kinetics, etc.
  - (Assuming you have some data!)
- Versatility of statistical approach makes it compatible with other kinds of process innovation (cell line engineering, media optimization, control of other variables)



# Broader Vision of ML in bioprocess optimization



Thank You! Let's Connect...  
Email: akhiljalan@utexas.edu



#### References

1. Glacken, Michael W. "Catabolic control of mammalian cell culture." *Bio/technology* 6.9 (1988): 1041-1050.
2. Matthews, Thomas E., et al. "Closed loop control of lactate concentration in mammalian cell culture by Raman spectroscopy leads to improved cell density, viability, and biopharmaceutical protein production." *Biotechnology and bioengineering* 113.11 (2

