

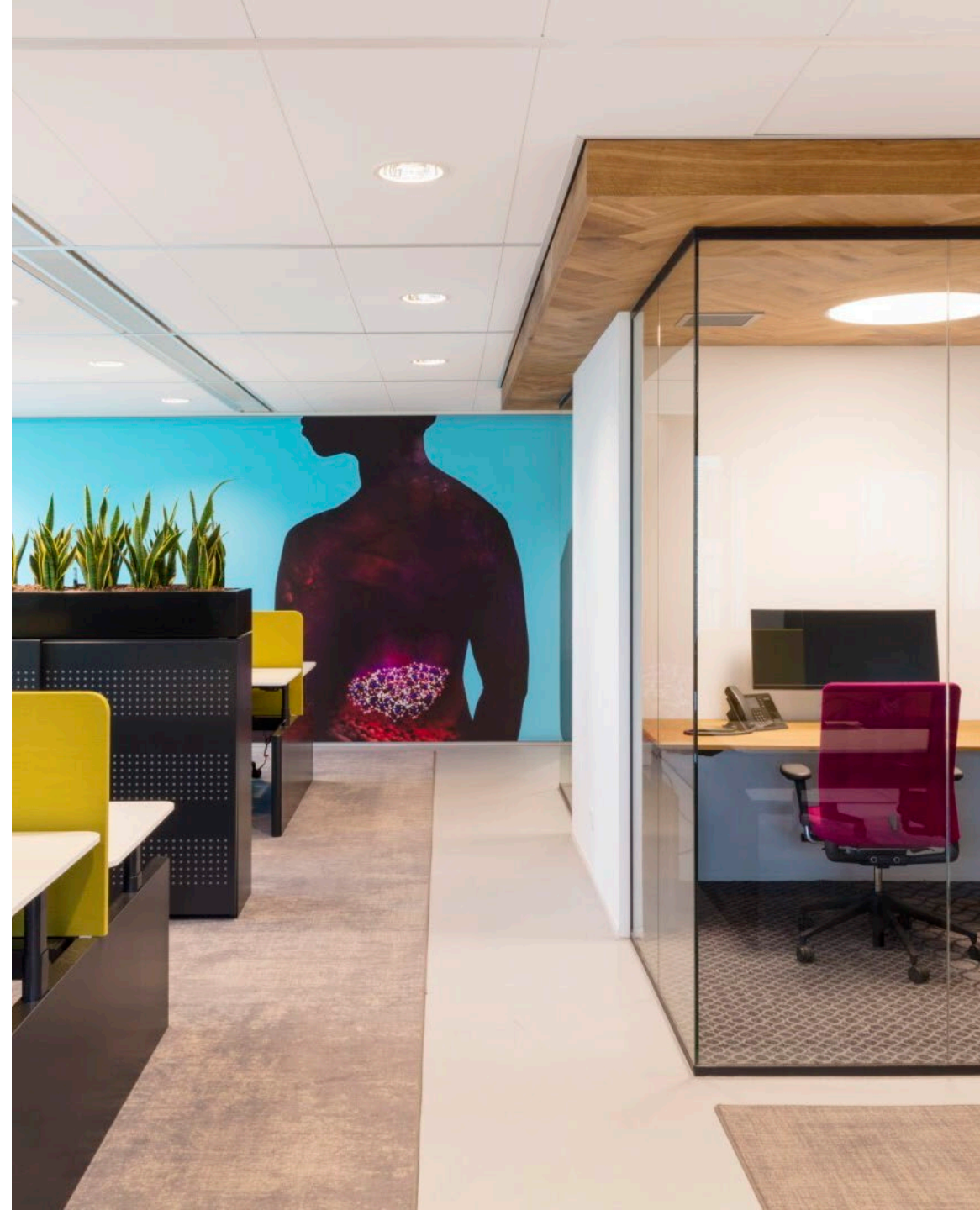
# How do theorists and experimentalists interact in a biopharmaceutical company?

Ken Lee <sup>1</sup>, Chris Thompson <sup>2</sup>

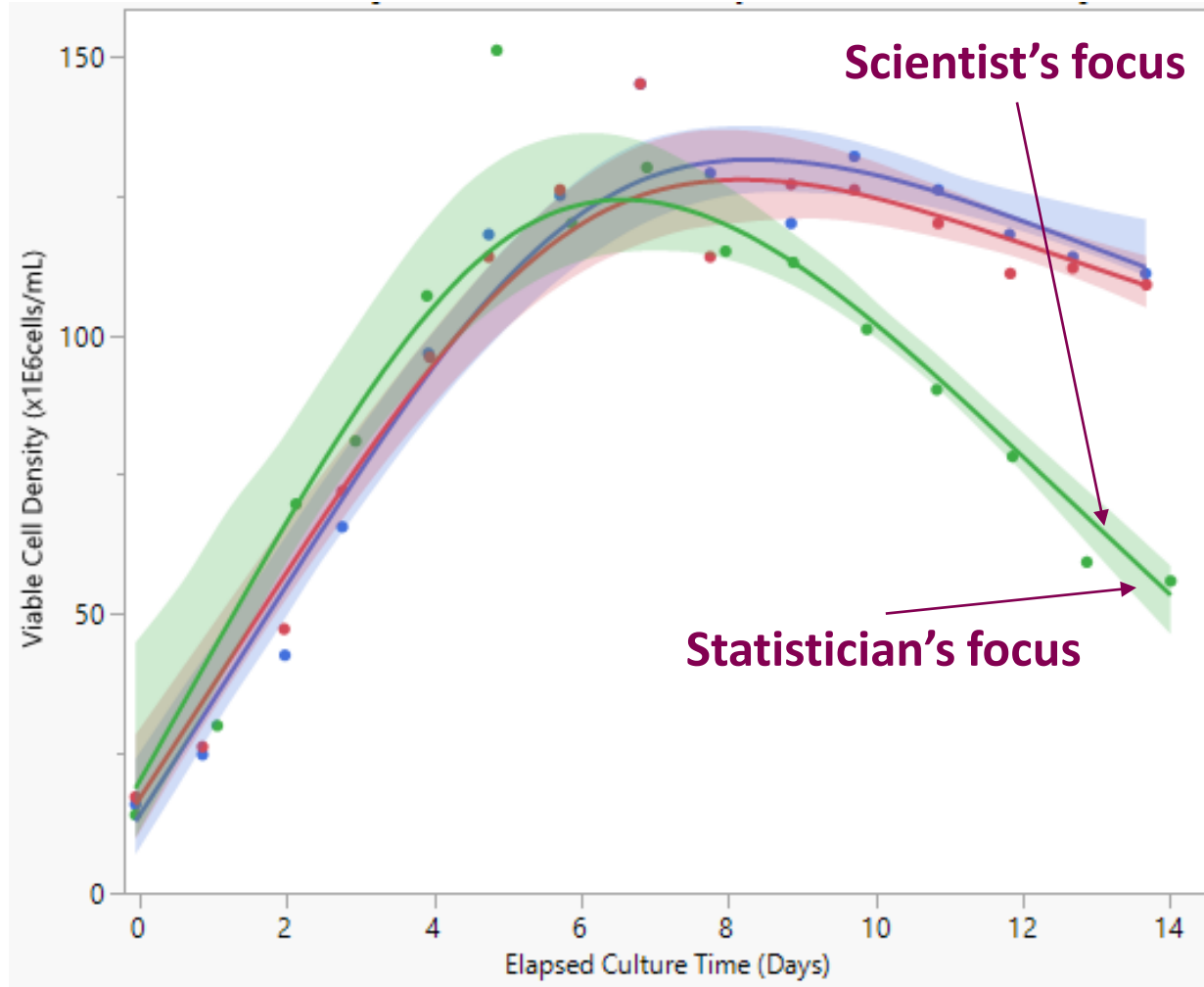
<sup>1</sup> Bioprocess Technologies & Engineering, BioPharmaceutical Development, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, US

<sup>2</sup> Data Science & Modelling, BioPharmaceutical Development, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, US

14 November 2024



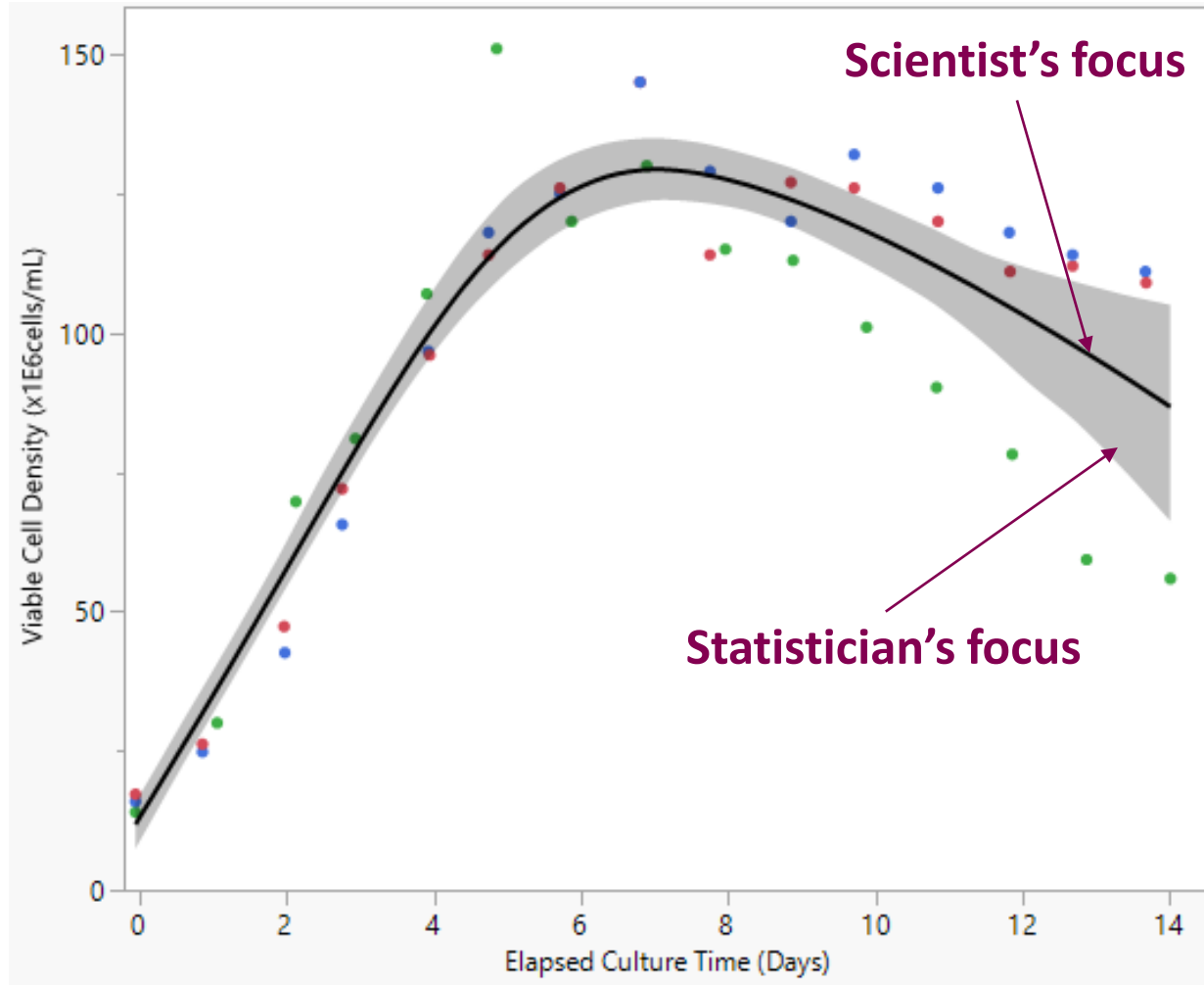
# Different viewpoints between statisticians and scientists



- Scientists focus on the mean
- Statisticians look at the mean and the confidence



# Data needs to be given context

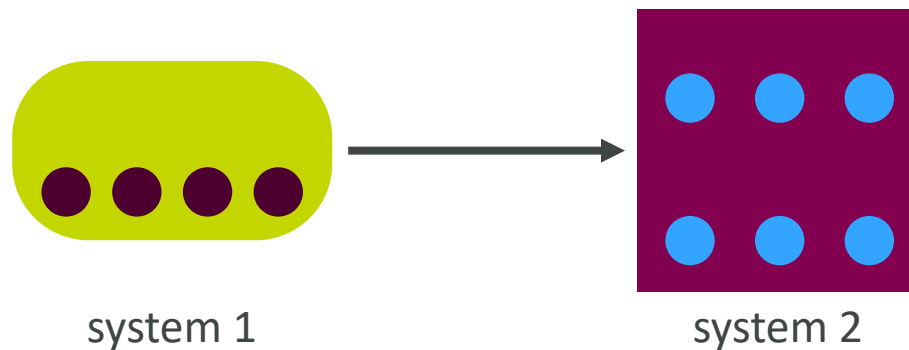
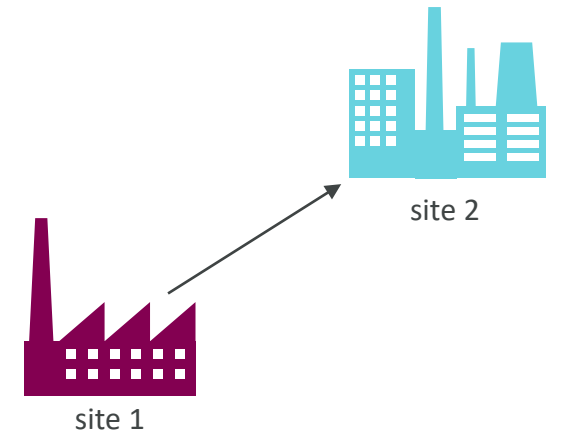
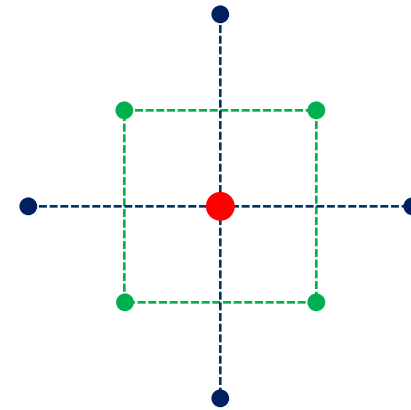


- However, the data needs to be given context



# Where do statisticians and engineers traditionally meet?

- CMC characterisation studies
  - Multiple controls
  - Multivariate studies
  - Excursion studies
- CMC comparability, analytical or otherwise

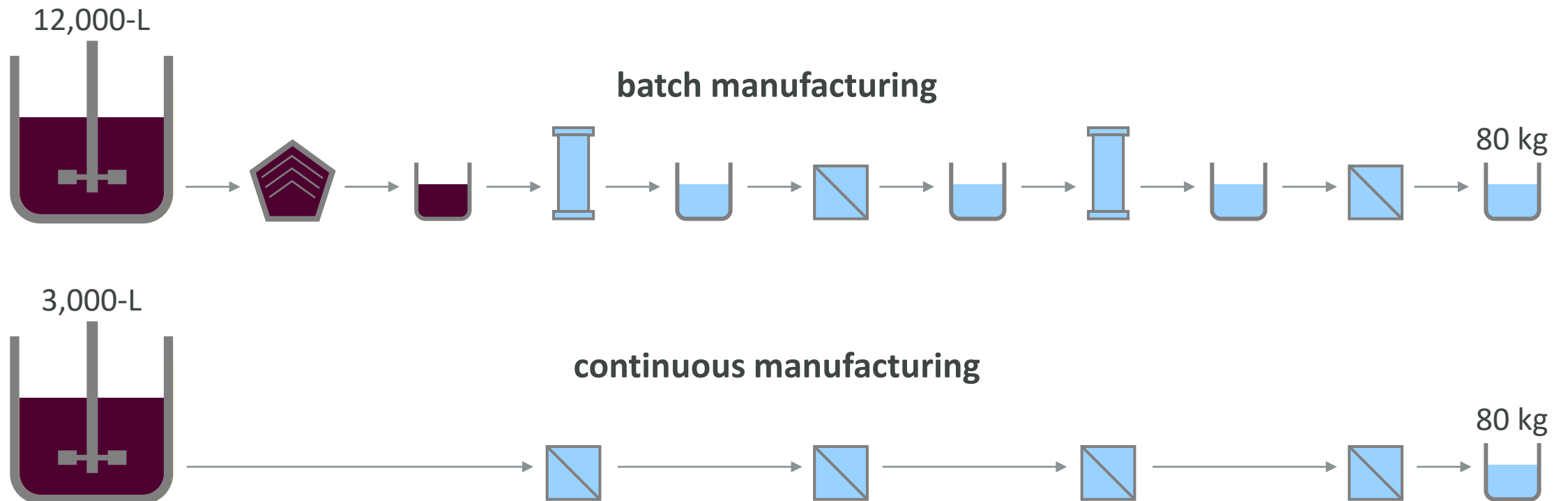


- Where do we not meet?
    - One-off experiments
    - Directional studies
- } Technology development



# What is Bioprocess Technologies & Engineering?

- AstraZeneca historically a biopharmaceutical manufacturer focusing on batch manufacturing
- Bioprocess Technologies & Engineering tasked with bringing continuous manufacturing to AstraZeneca



# How does this change interactions between the two groups?

## Existing ways of working – no change

- Characterisation studies
  - With new variables
- Analytical comparability

## Adapting ways of working

- Scale-down modeling
  - New variables with unknown effects
  - Existing variables could have new effects
- Clone selection strategy
  - Batch clone selection for a continuous manufacturing process

## New ways of working

- Leveraging online data to probe for new insights
- Leveraging prior knowledge in batch manufacture
- PAT / Raman modelling
  - Identifying significant highlights and features that are highly correlated to a measured analyte



# Case Study

## Scale-down cell culture model for continuous manufacturing

Data from Zayla Schaeffer and John Murphy

Slides adapted from Zayla Schaeffer and John  
Murphy, first presented at BPI-Boston 2024



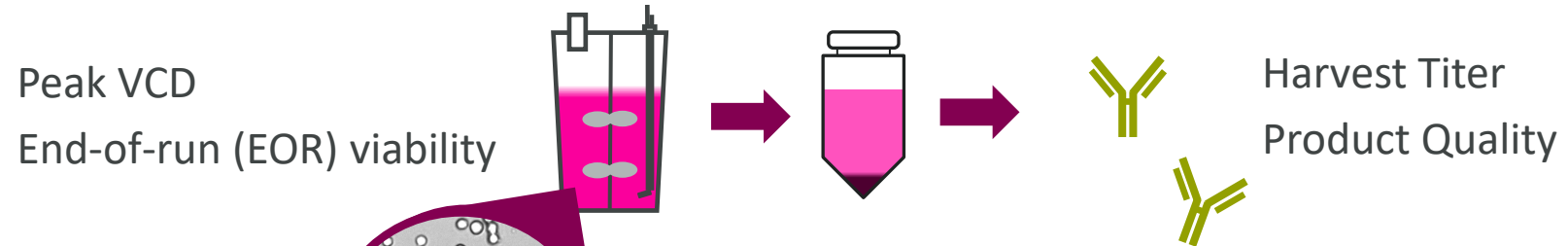
# Why use a different scale-down model?

- More efficient resource usage
  - More conditions per scientist
  - Less raw material usage
- Key outputs
  - Demonstrate the proposed scale-down platform is effective for 3+ molecules
- Some caveats to using the proposed scale-down strategy
  - Different equipment operating modes
  - Changes in cell culture environment
- Considerations for the experimental design
  - Molecules all use different cell clones
  - Experiment durations are long (14+ days)

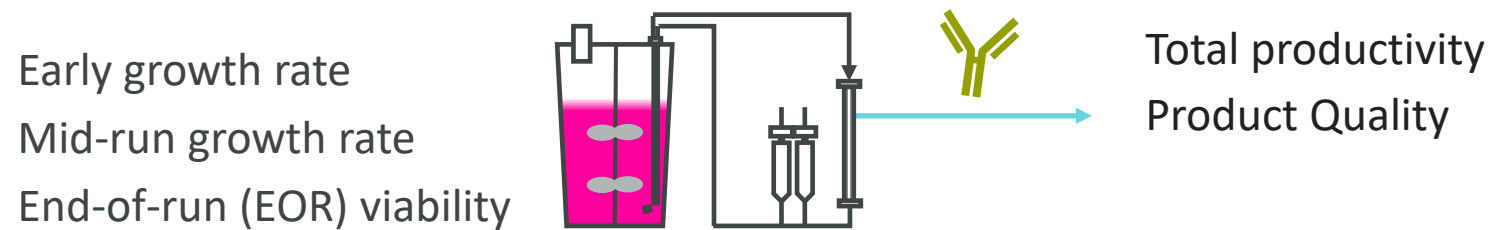


# Transforming scaling metrics for fed-batch culture into perfusion equivalents

## Fed-batch:



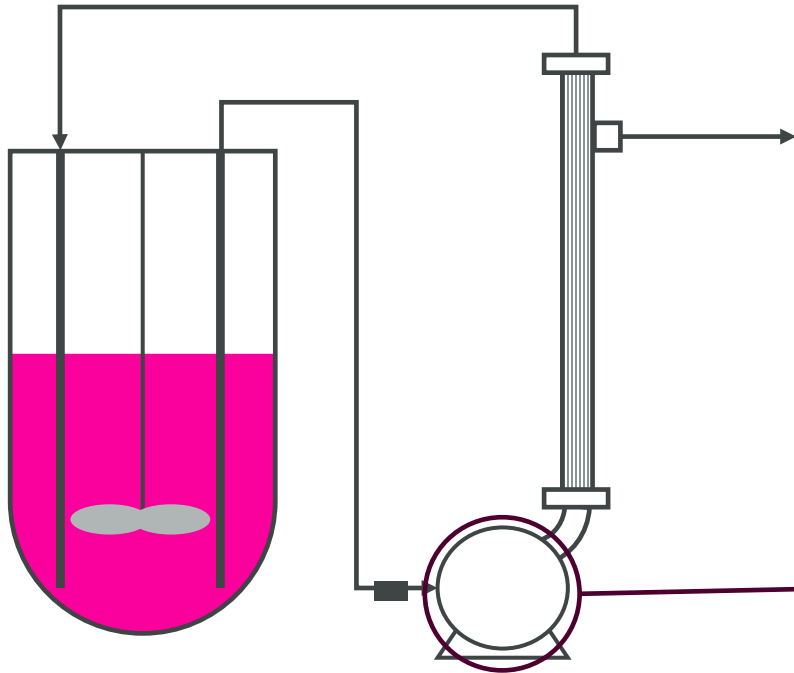
## Perfusion:



Slide adapted from [Zayla Schaeffer](#) and John Murphy  
First presented at BPI-Boston, 2024



# Recirculation loop varies between scales



**3-L+ scale**

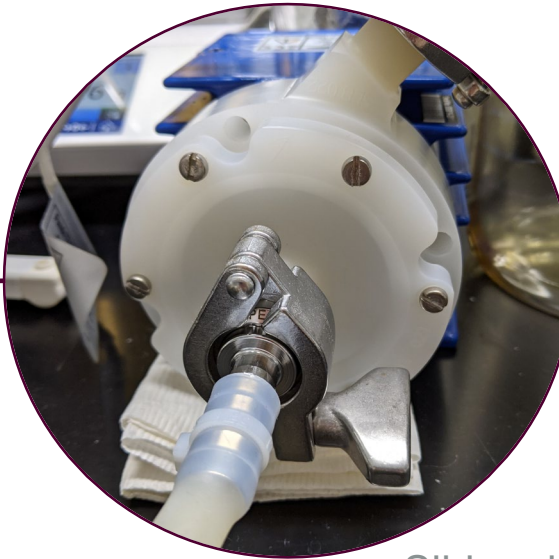
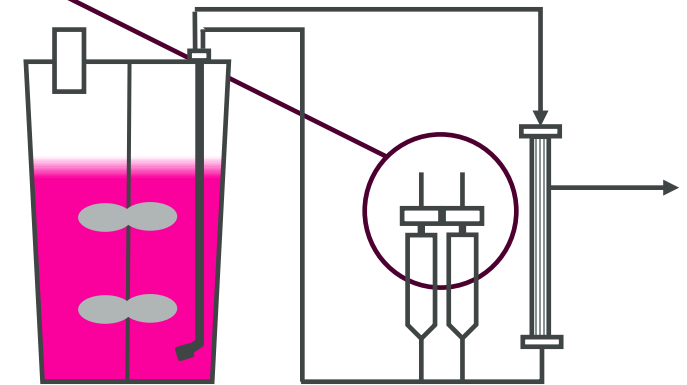
Centrifugal pump spinning at RPM range of 700-2000  
RPM controlled by in-line flow meter reading



Air-enabled pumps: push and pull culture into each chamber

Not a significant source of shear stress

**ambr250 scale**



Slide adapted from [Zayla Schaeffer](#) and John Murphy  
First presented at BPI-Boston, 2024



# The dataset needs to be given a context

Opportunistic gathering of comparison data between representative target scales and the test scale

## Dataset contained

- 5 total projects
- 11 clones
- 10 input variables











## Criteria

- 5 performance metrics



## Context

- Dataset is a representation of a larger dataset
- Clones are linked to projects and hosts
- Not all data is equal
- Statistically significant may not be practically significant

## Available data

	Target scale	Test scale
Project 1		
Project 2		
Project 3		
Project 4		
Project 5		

## Legend

-  Color indicates different clones
-  Count indicates number of runs

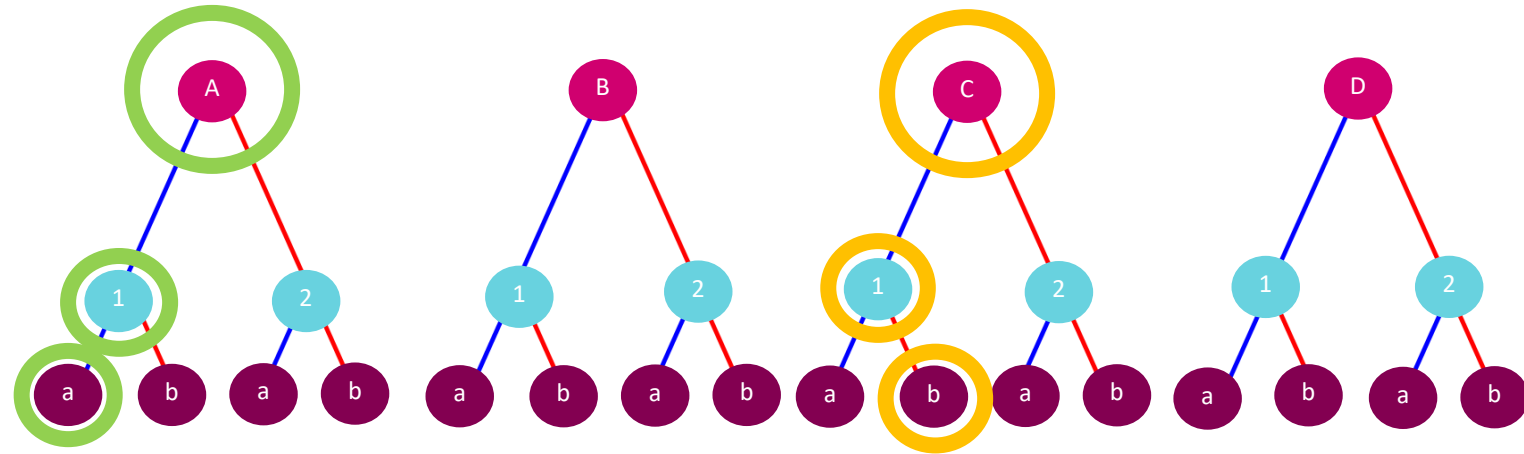
Slide adapted from [Zayla Schaeffer](#) and John Murphy

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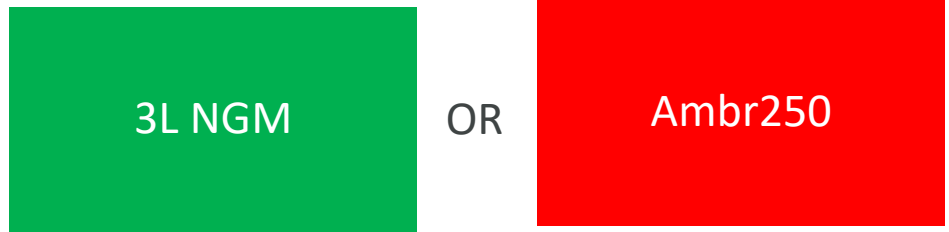


# Linear Model: Nesting & Hierarchical Structure

Data #1	Data #2
Host A	Host C
Project 1	Project 1
Clone A	Clone B
Target scale	Test scale



- Host
- Project
- Clone ID
- Scale

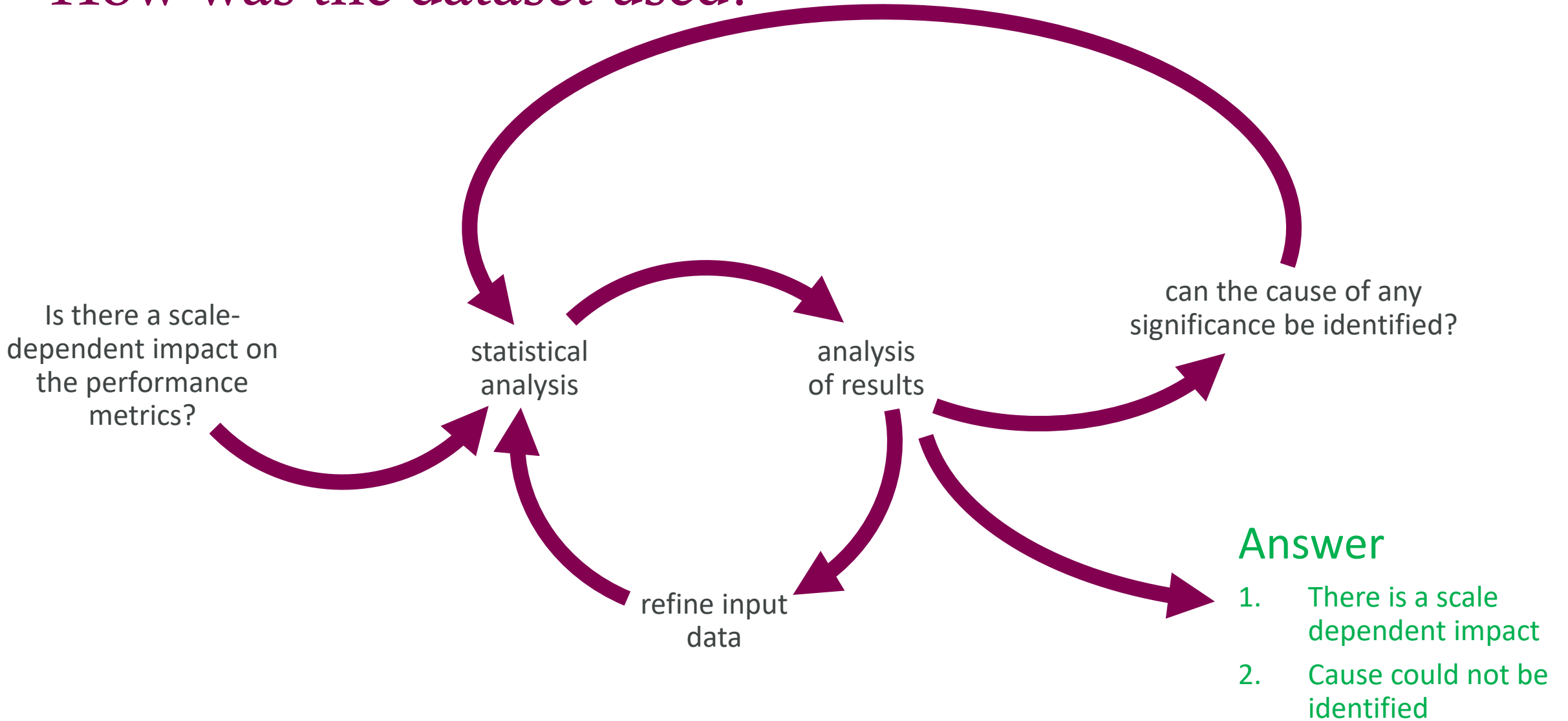


Scale
 + ●
 + ●
 + ●
 = Prediction

Slide from [Zayla Schaeffer](#) and John Murphy



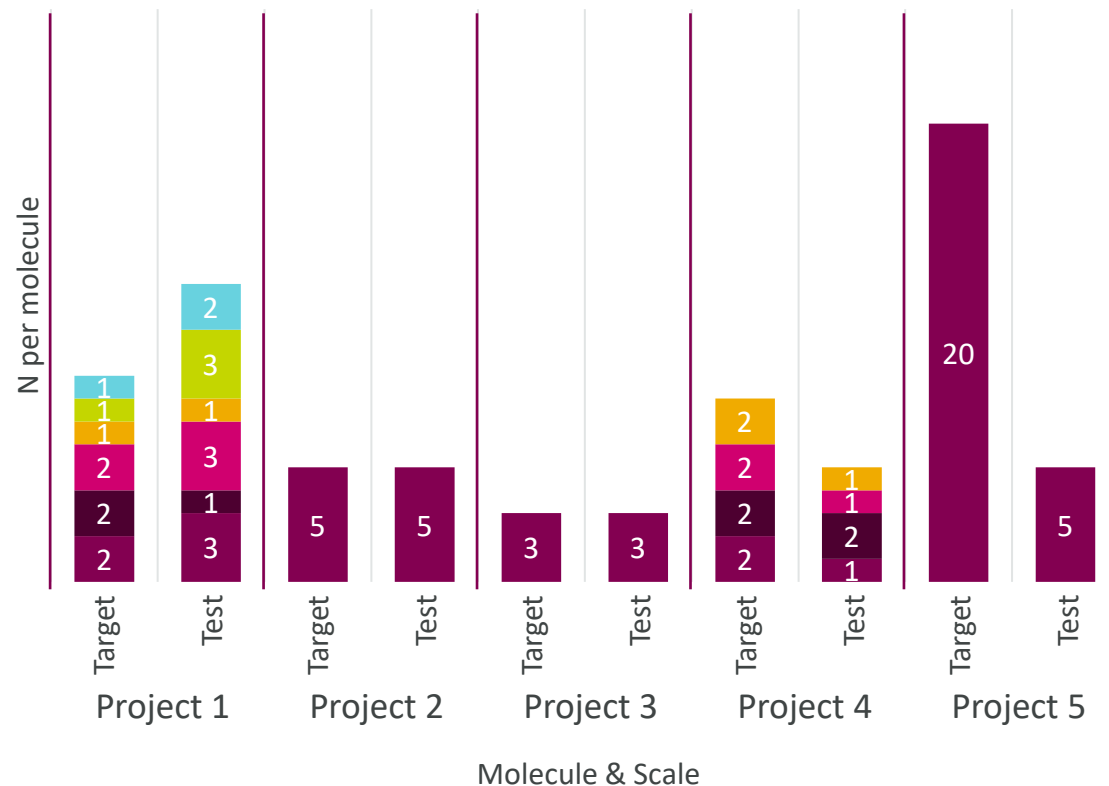
# How was the dataset used?



# Final dataset included in analysis

At a glance:

- 5 different projects
- 45 total N for 3L
- 31 total N for ambr250
- 13 different host-project-clone pairings
- Between 1-20 replicates per host-project-clone pairing
- Both datasets have most replicates with the same project
- A few end-of-run datapoints removed due to contamination and system errors
  - 6/400 test datapoints removed for contamination
  - 4/625 target datapoints removed for equipment errors



Slide adapted from Zayla Schaeffer and John Murphy



# Concluding remarks from a non-statistician

- Basic stats are easy
- Quantifying statistical significance can be very hard
  
- Collaboration is key to understanding the output of complex experiments



# Acknowledgements

Chris Thompson

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