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Automated foam control in single-use bioreactors using the single use foam probe

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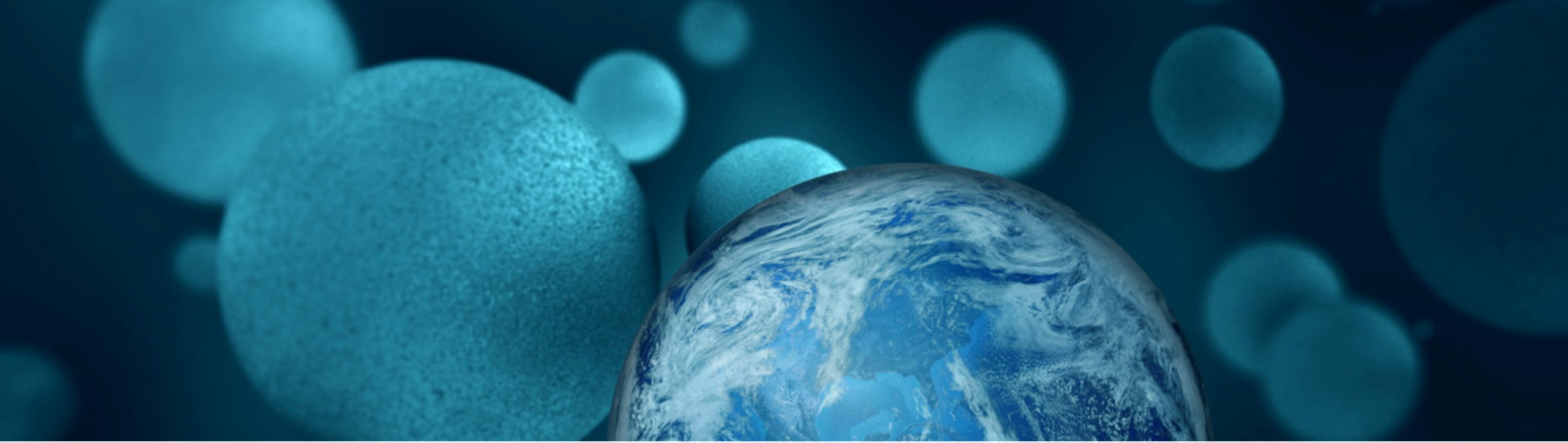

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Automated foam control in single-use bioreactors using the single-use foam probe

September 28, 2018

Jordan Cobia
Systems Design Engineer

Agenda

- Introduce Thermo Fisher SUT
- Foam and Antifoam
- Foam Probe Design and Application
- Cell Culture Application Data
- Conclusion

Global Single-Use Manufacturing Footprint

Miami, OK

- All critical environment products and services
- ISO 9001:2008

Rochester & Fairport, NY

- Bioprocess rigid containers
- Cell Factory systems
- ISO 13485:2003
- FDA Registered

Cramlington, UK

- Bioprocess containers
- Single-use technologies
- Class 10,000/ISO 7 clean room

Roskilde, Denmark

- Cell Factory systems
- ISO 9001, ISO 13485
- FDA Registered

Logan, Utah

- BioProcess Containers
- Single-use technologies
- Class 10,000/ISO 7 clean room

Santa Clara, CA

- Controllers, sensors
- Vessels
- Class 10,000/ ISO 7

Matamoros, Mexico

- BioProcess Containers
- Single-use technologies
- ISO 13485
- cGMP standards

Millersburg, PA

- BioProcess Containers
- Single-use technologies
- ISO 13485
- cGMP standards

Suzhou, China

- Bioprocess rigid containers
- Cell Factory systems
- ISO9001, 14001, 13484

https://www.timesunion.com/news/article/Fire-supression-foam-lets-loose-at-airport-12303557.php

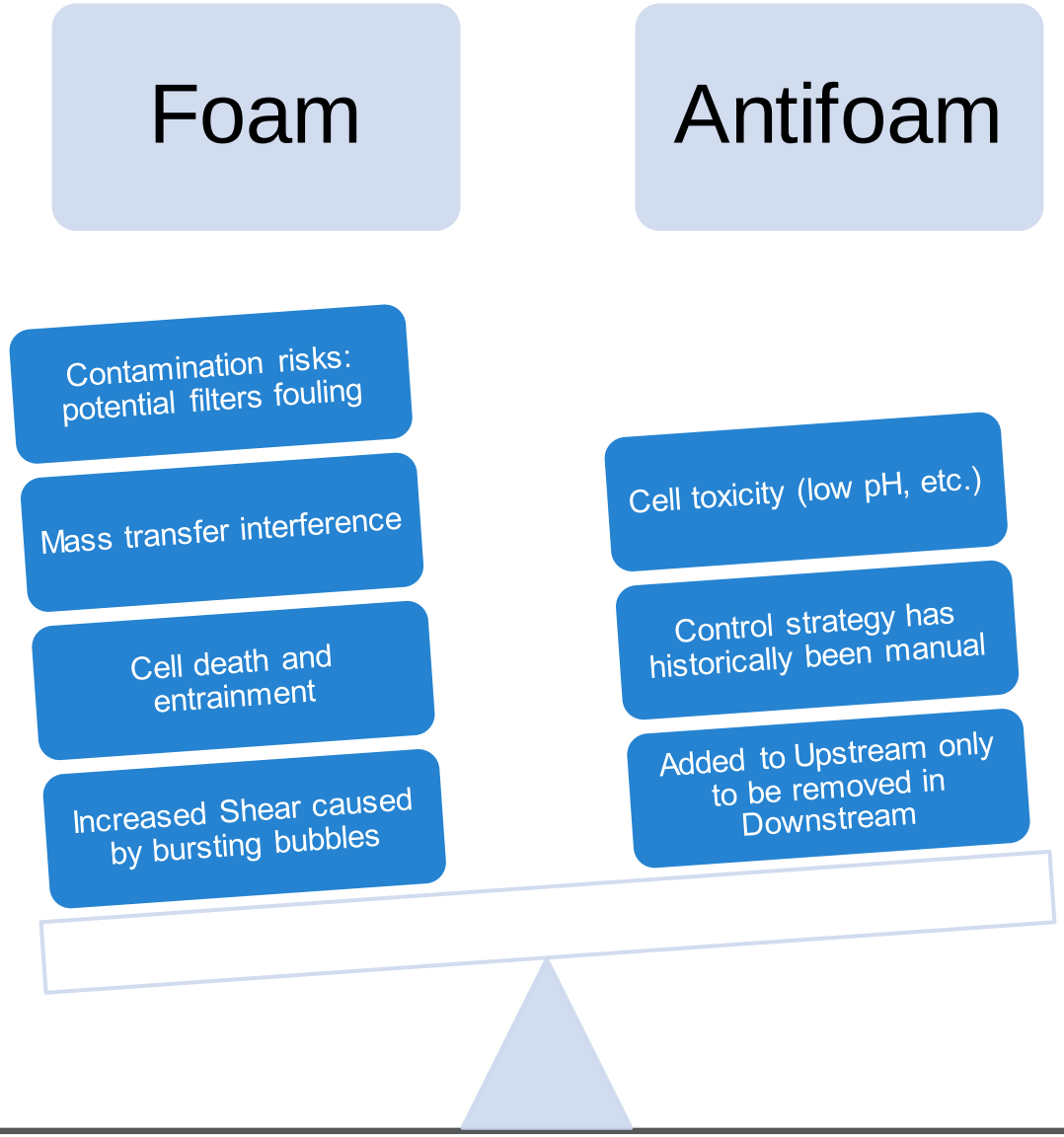
://www.sfgate.com/bayarea/article/Foam-spills-out-of-San-Jose-airport-hanger-and-10623824.php

Foam and Antifoam Risk Analysis

Antifoam use is a necessary evil in bioprocessing. The benefits far out weight the risks.

Antifoams are used across many industries:

- Chemical
- Oil & Gas
- Plastic Recycling
- Agriculture and Crop Care
- Pulp & Paper
- Water Treatment
- Food

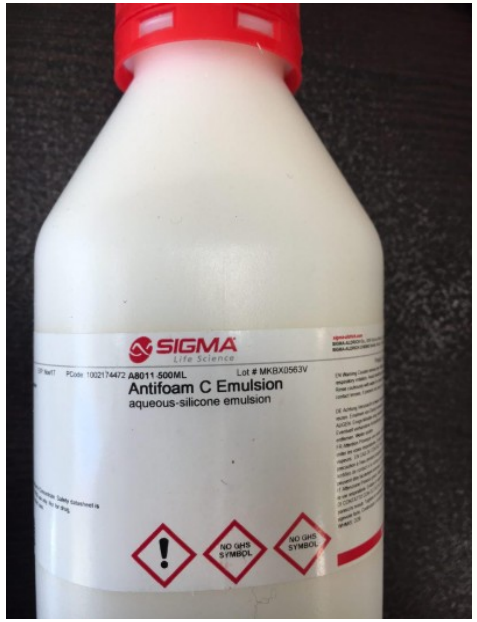


Status Quo for Foam Control

Stainless steel reactors typically employ mechanical foam breaker (microbial), this is difficult to translate into a scalable solution. Chemical de foaming agents are required.

Many types of antifoam emulsions are available that are either autoclave friendly often requiring dilution or irradiated in a ready to use format.

Typically antifoam is dosed in a very manual manner. Dosing based on time/volume or when the operator observers a particular level of foam in the vessel is not uncommon.



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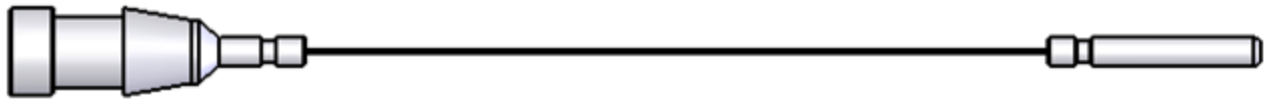
Antifoam Control

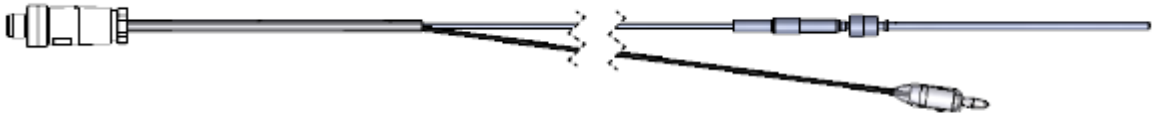
- The single use foam probe is a conductivity based probe that outputs a numerical value from 0 to 100
- Historically this has only been used as a last case resort on the SUF to prevent filter fouling and it has worked extremely well

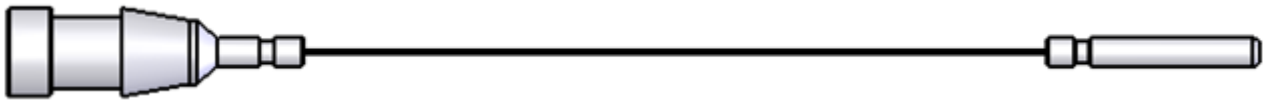
Foam Probe Process Value	Physical Condition
0%	Foam probe not connected
~25%	Foam probe exposed to air, static position
25% to <100%	Foam probe exposed to air/liquid mixture(foam)
100%	Foam probe submerged or bridged connection



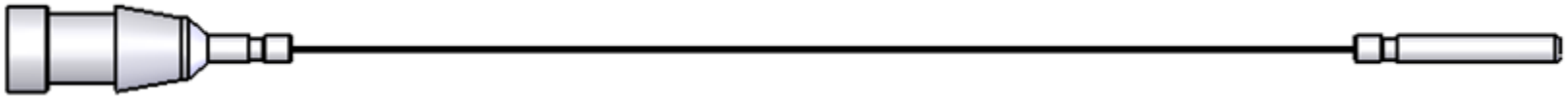
Foam Probe Design and Integration

- Foam Probe is made of small gauge Nitinol memory metal and SS316L
  - Allow for flexible shipping and fabrication
  - Small gauge wire – unique design minimize surface area on the lead to eliminate false readings due to fouling

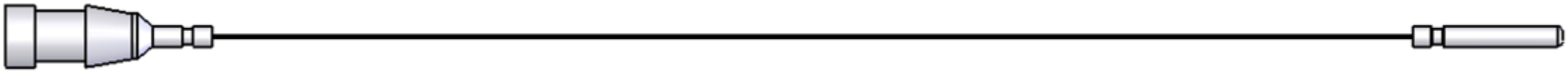




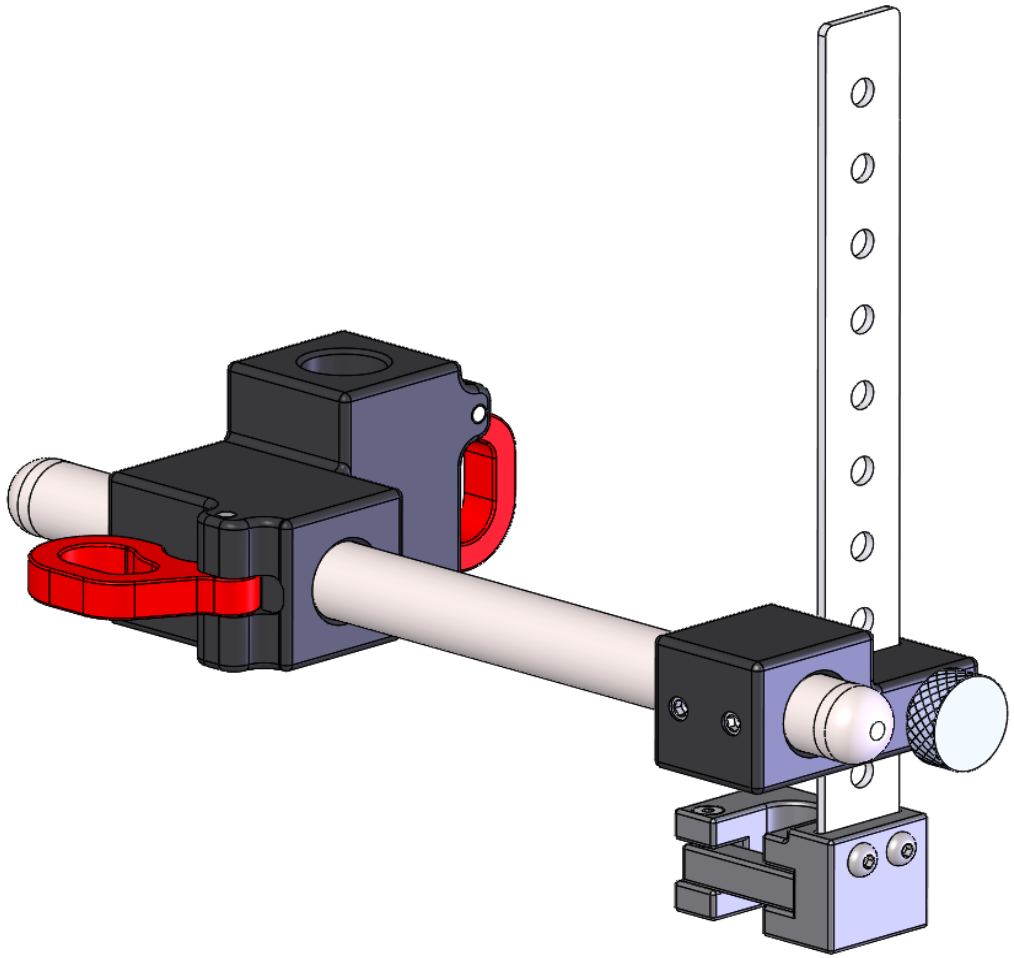
- 50L, 100L, and 250L SUB Foam Probe

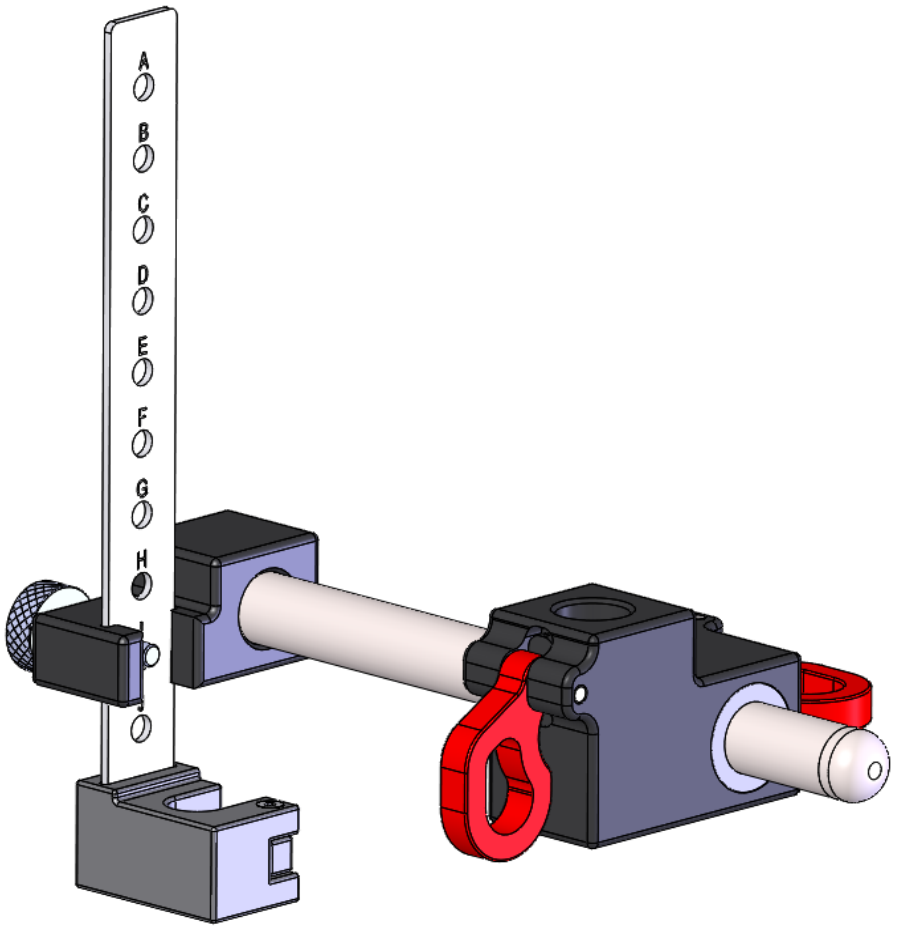


- 500L and 1000L SUB Foam Probe

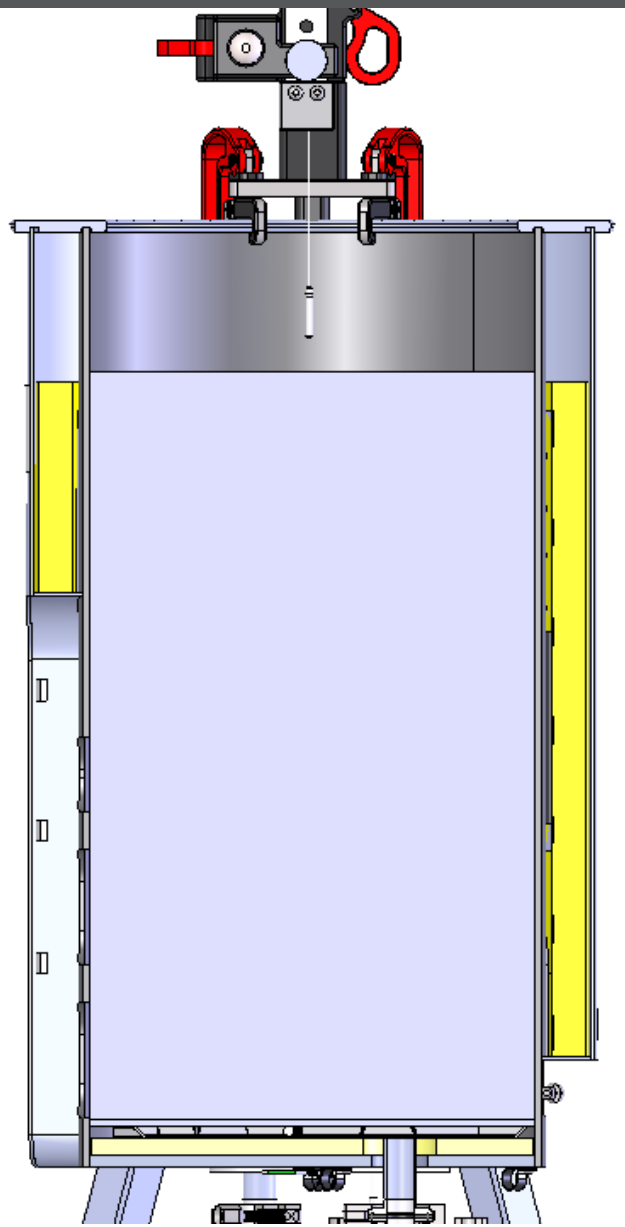


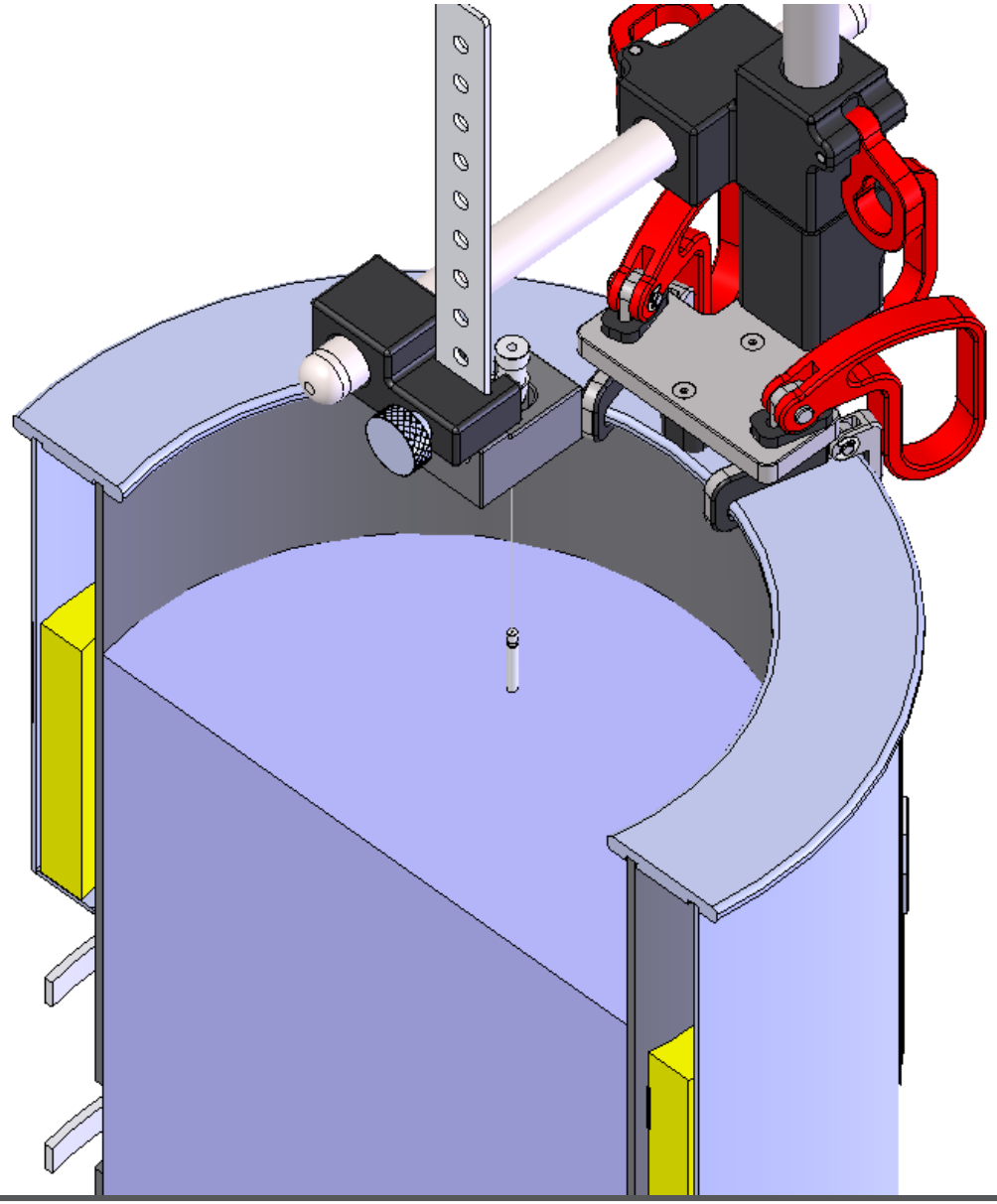
- 2000L SUB Foam Probe



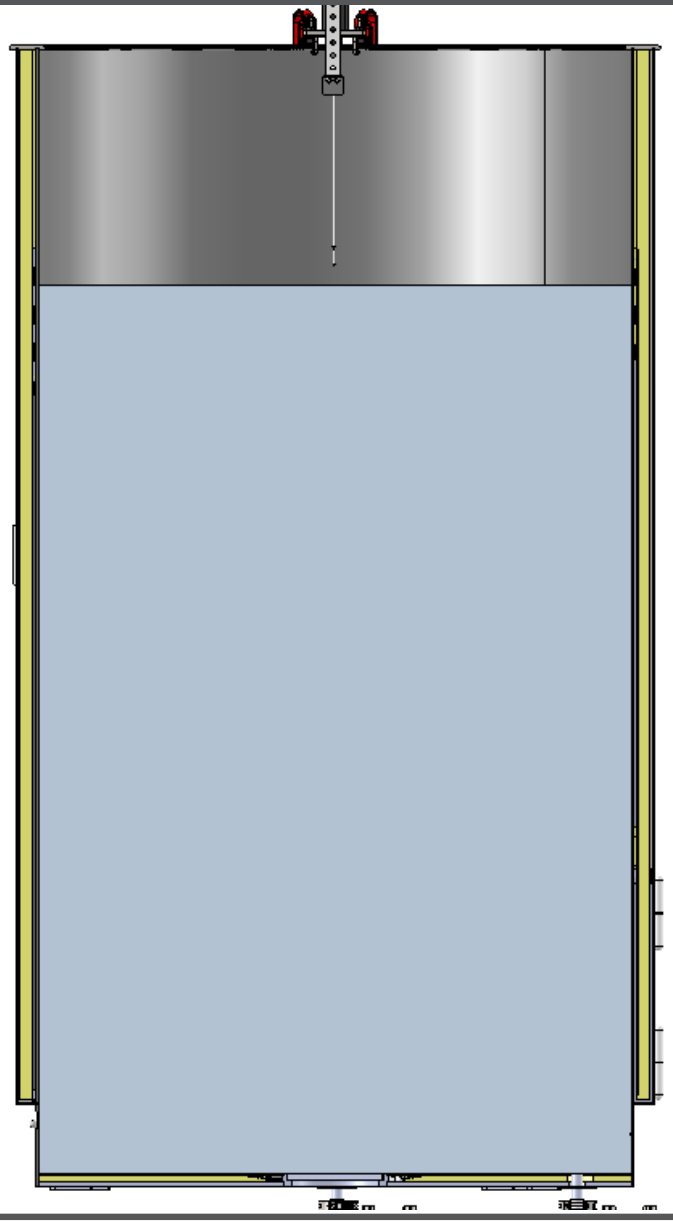


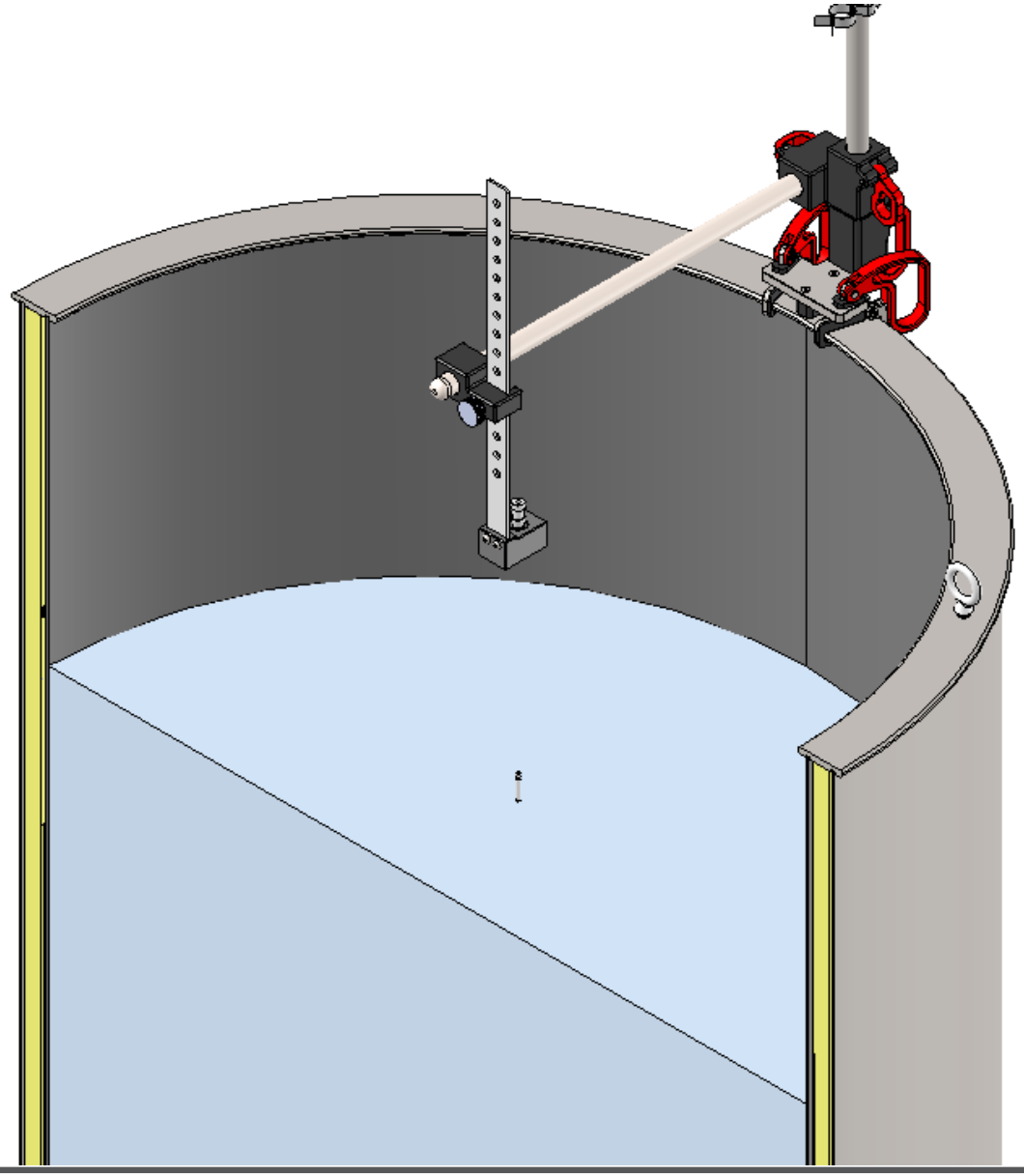
50L S.U.B. at 100% working volume





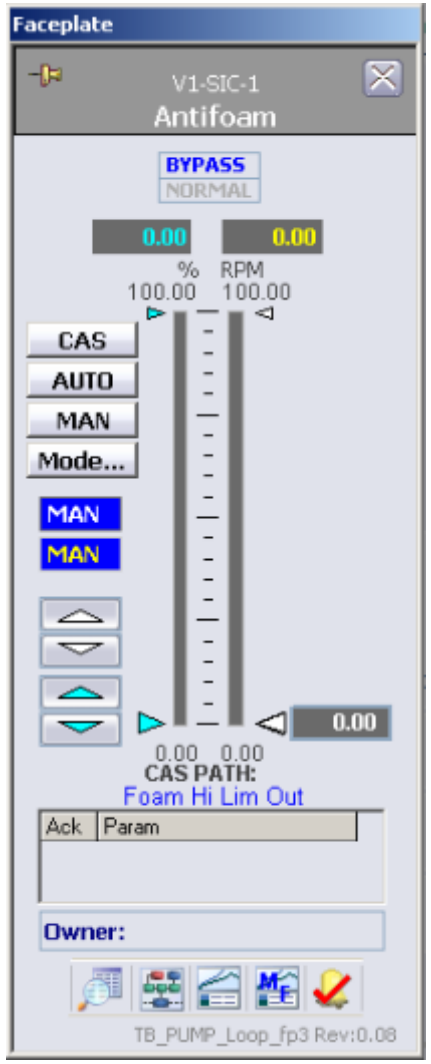
2000L S.U.B. at 100% working volume

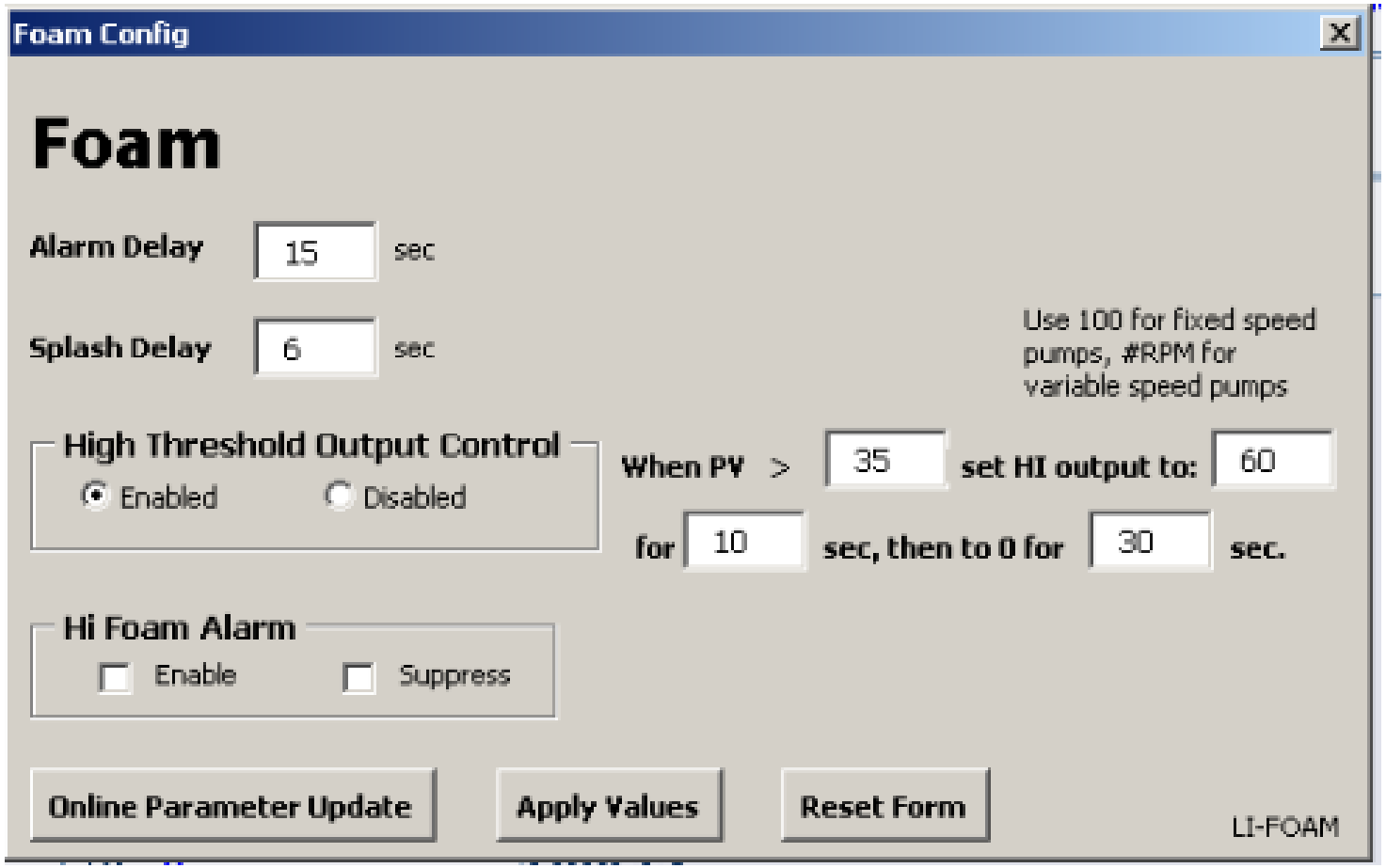




Foam Probe Control

- Alarm Delay- Sets the time (in seconds) before an alarm is activated
- Splash Delay— Sets the time (in seconds) during which the alarm is prevented from being triggered, which allows a temporary contact with foam





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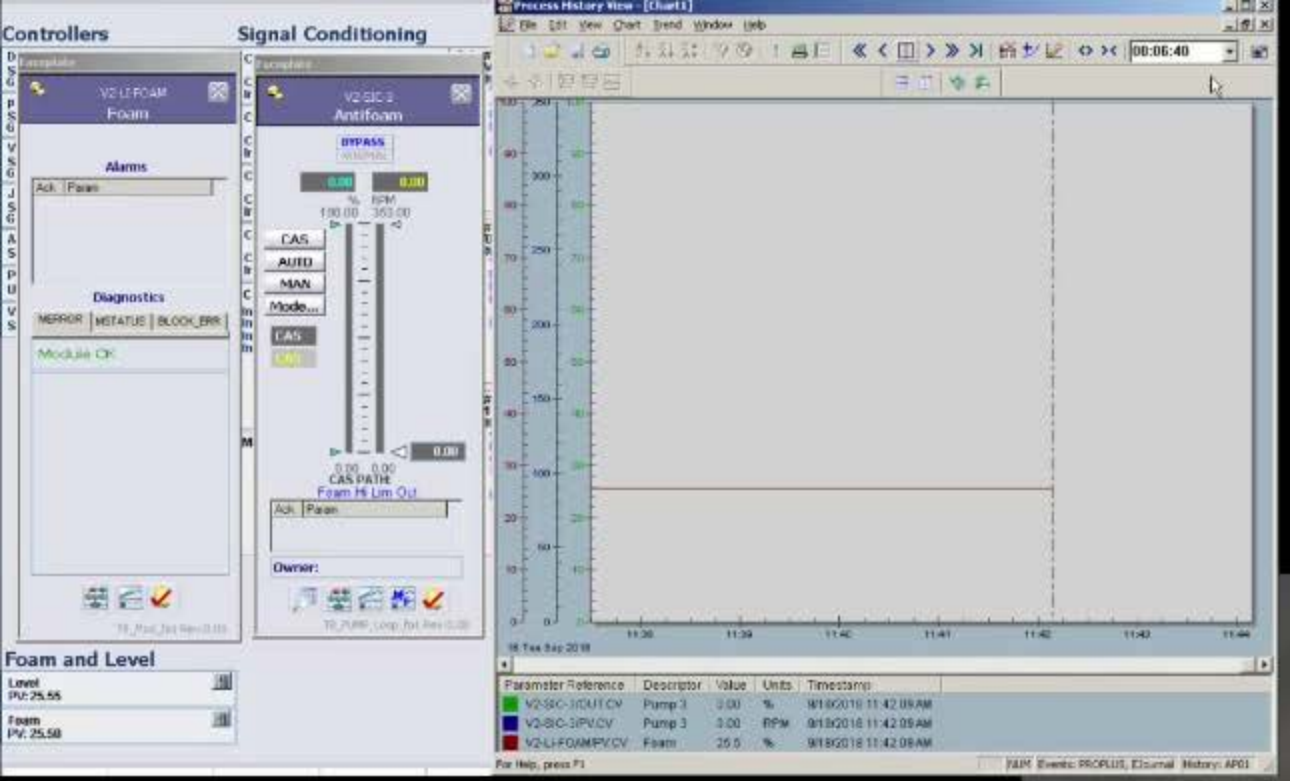
Foam Control
50 L S.U.B.

Anti-Foam Solution

Foam Probe



DeltaV Controller Screen Output

Cell Culture Results

50 L S.U.B. Side-by-Side Fed Batch

Standard gassing strategy

50 L S.U.B. Perfusion

Aggressive perfusion application

50 L S.U.B. Side-by-Side Fed Batch

Aggressive gassing strategy

0.1 VVM total gas flow

1000 L S.U.B. Fed Batch

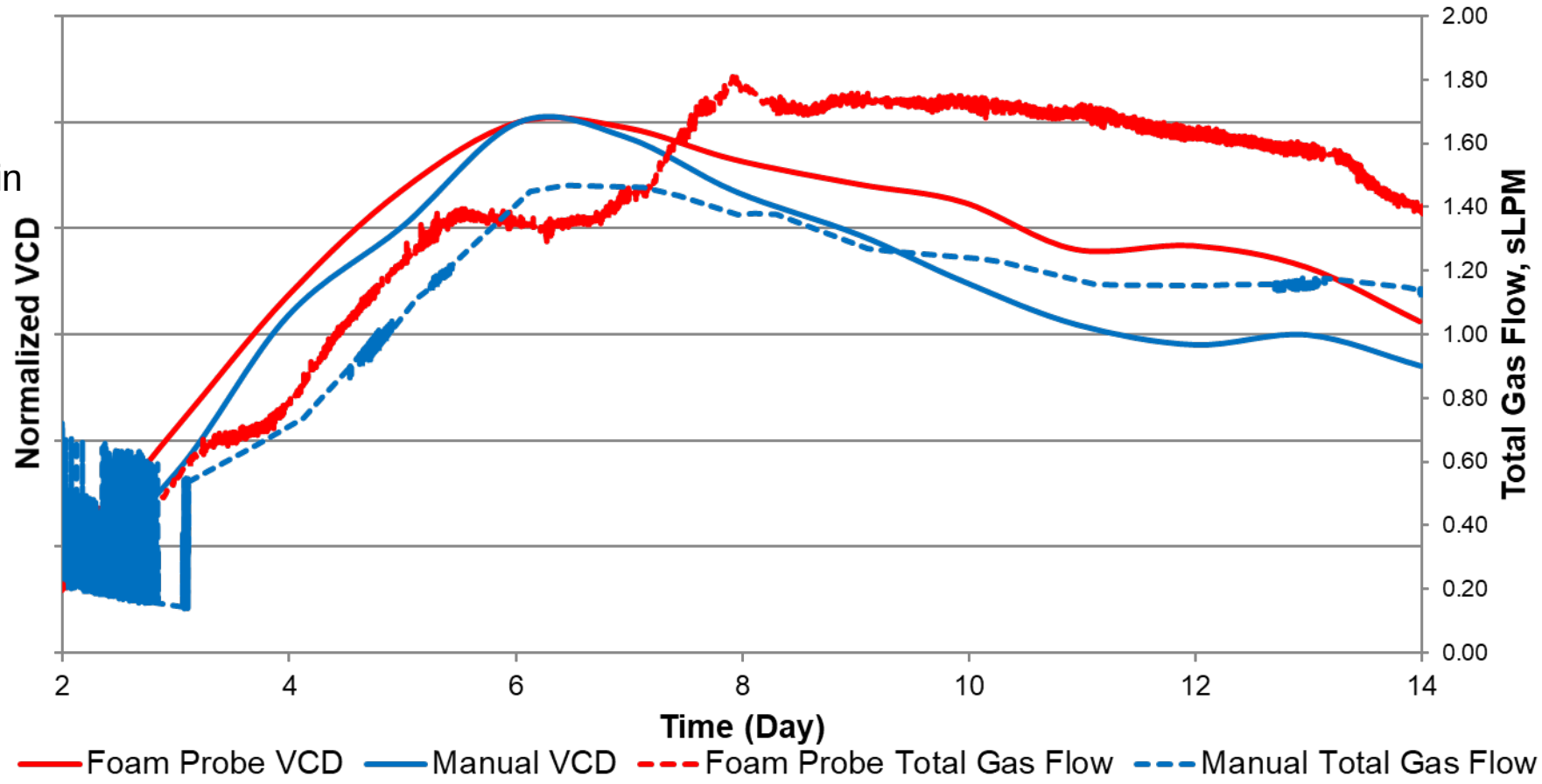
Aggressive gassing strategy

0.1 VVM total gas flow

Goal: Demonstrate scalability of the foam probe across multiple S.U.B. sizes and its application to aggressive processes

50 L S.U.B. Side-by-Side Fed Batch Results

- Gassing strategy
  - 30% DO
    - N2/O2 as needed to maintain setpoint
  - pH D0-3, 7.2; D3-14 7.0
    - CO2 input
- Foam Control
  - Controlled by foam probe
  - Manually controlled via automated dosing



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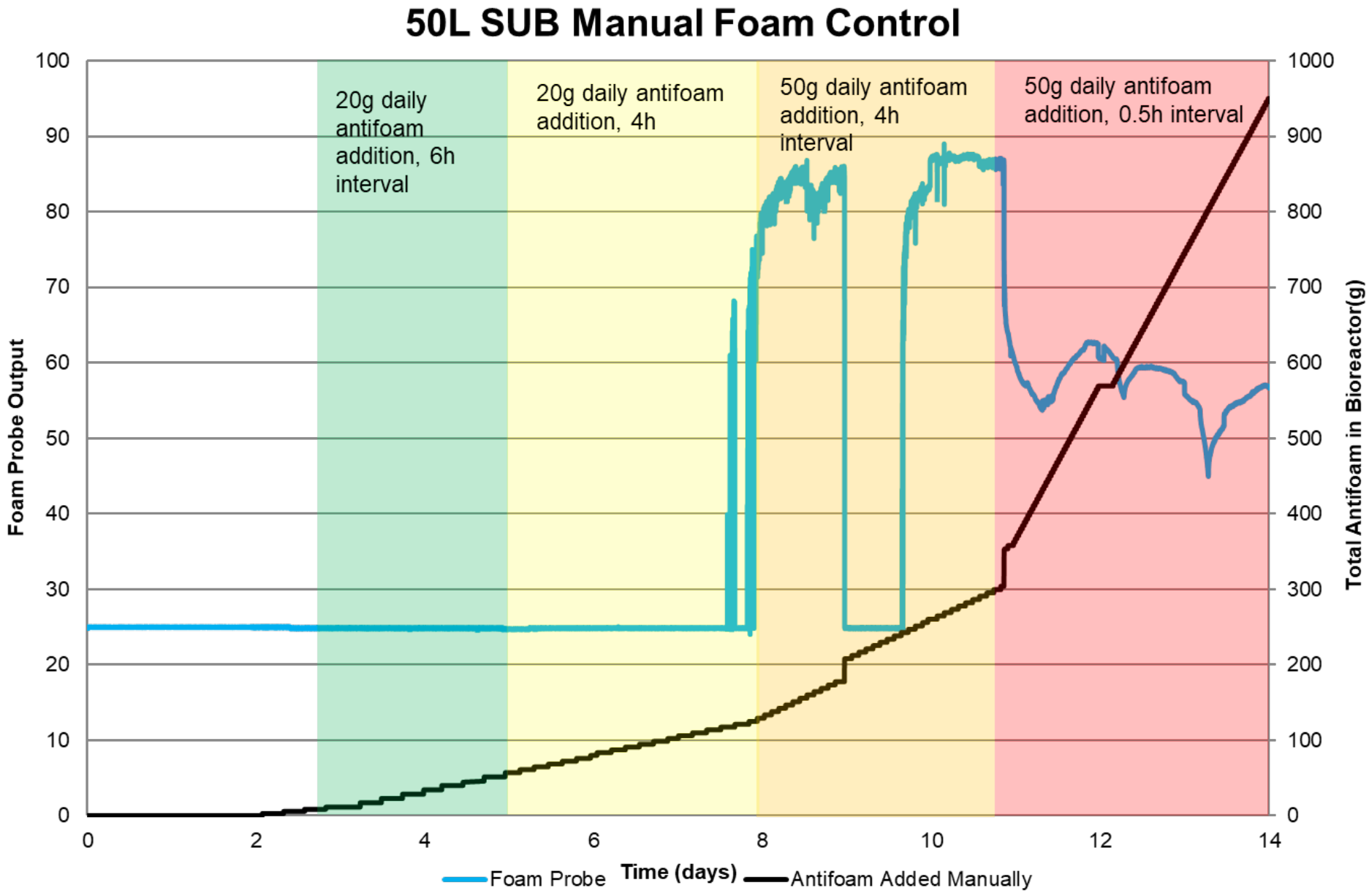

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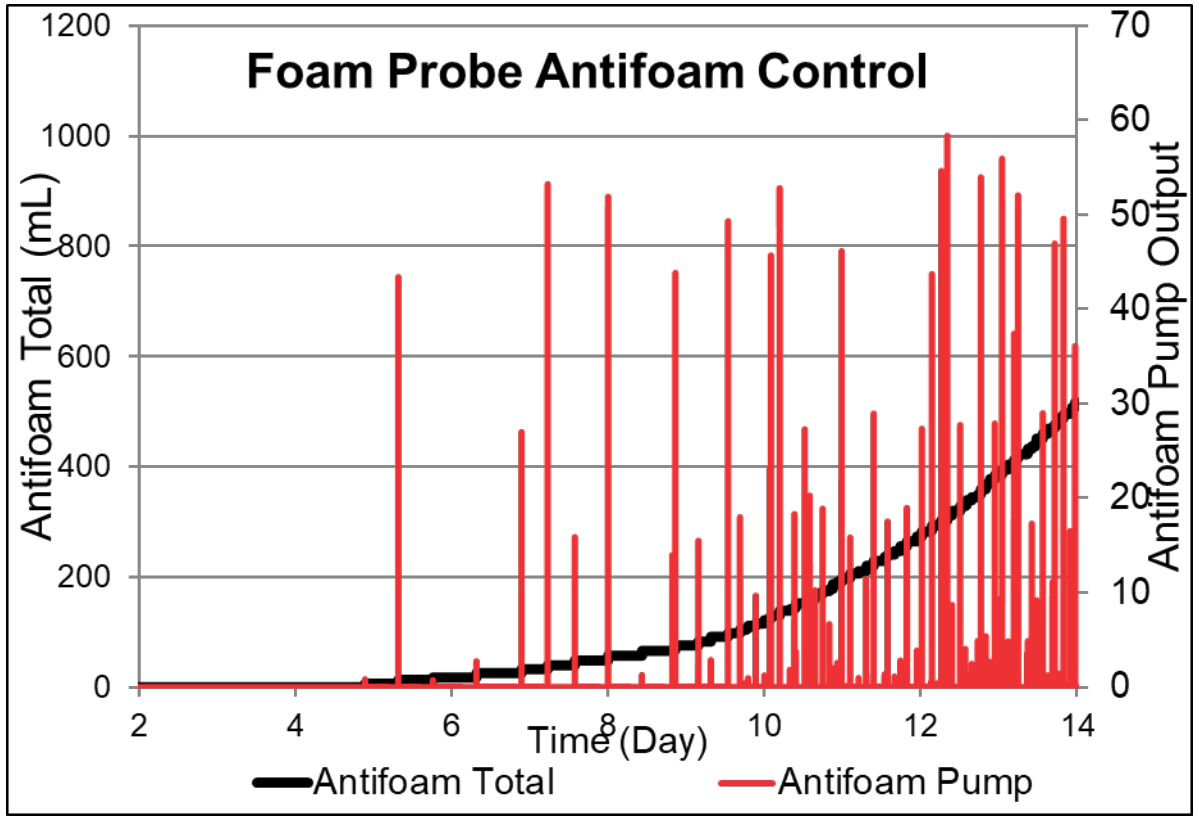
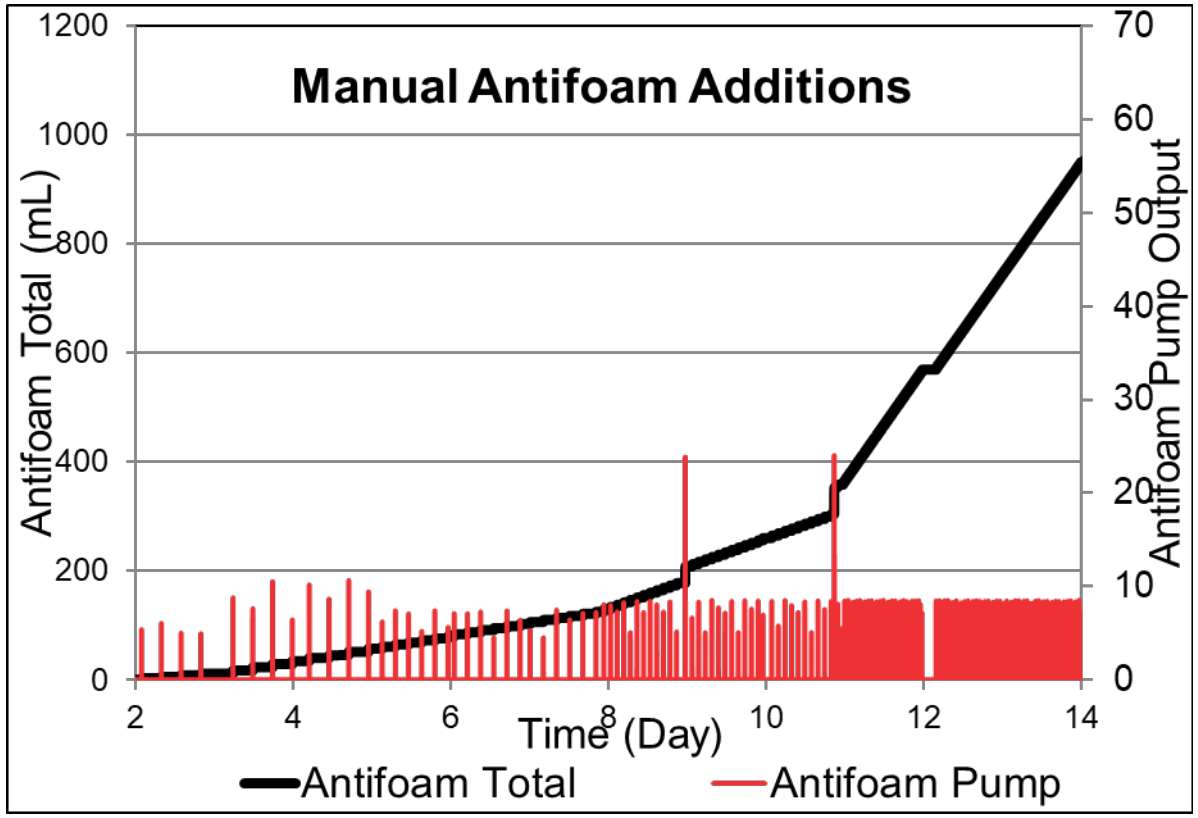
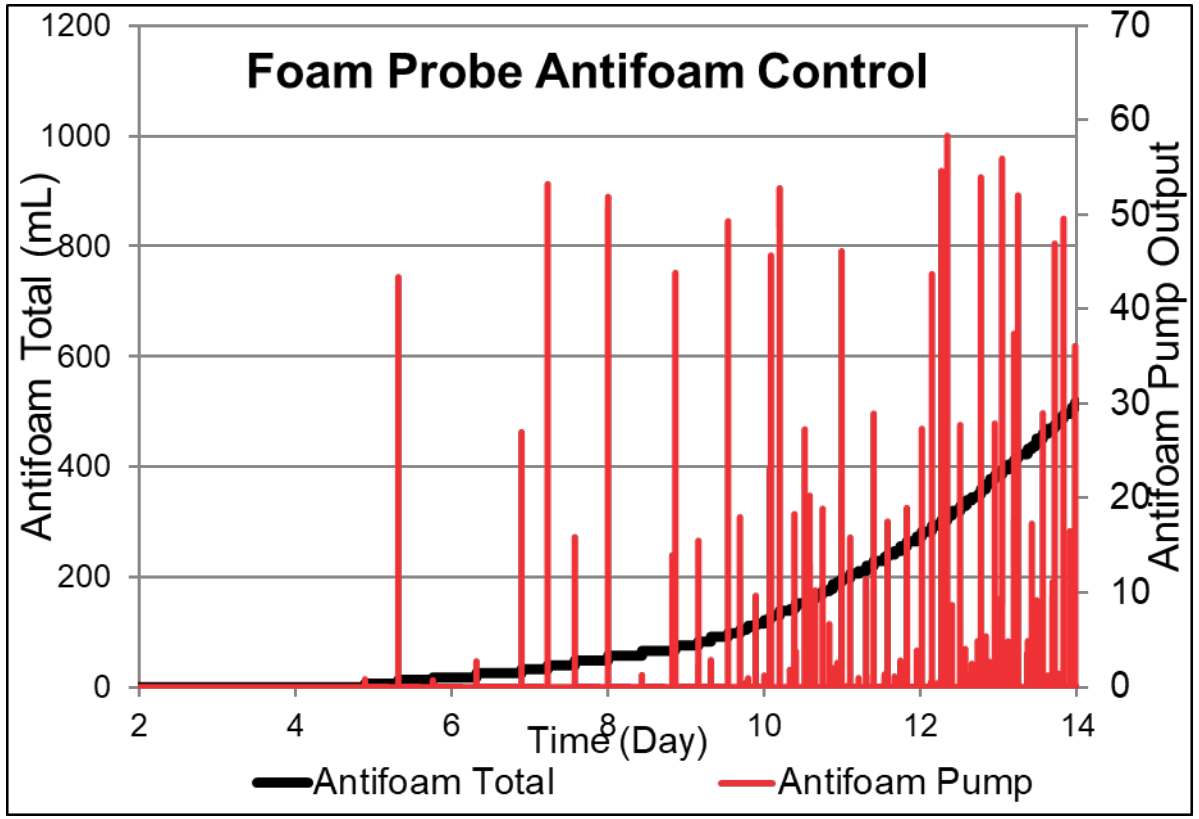
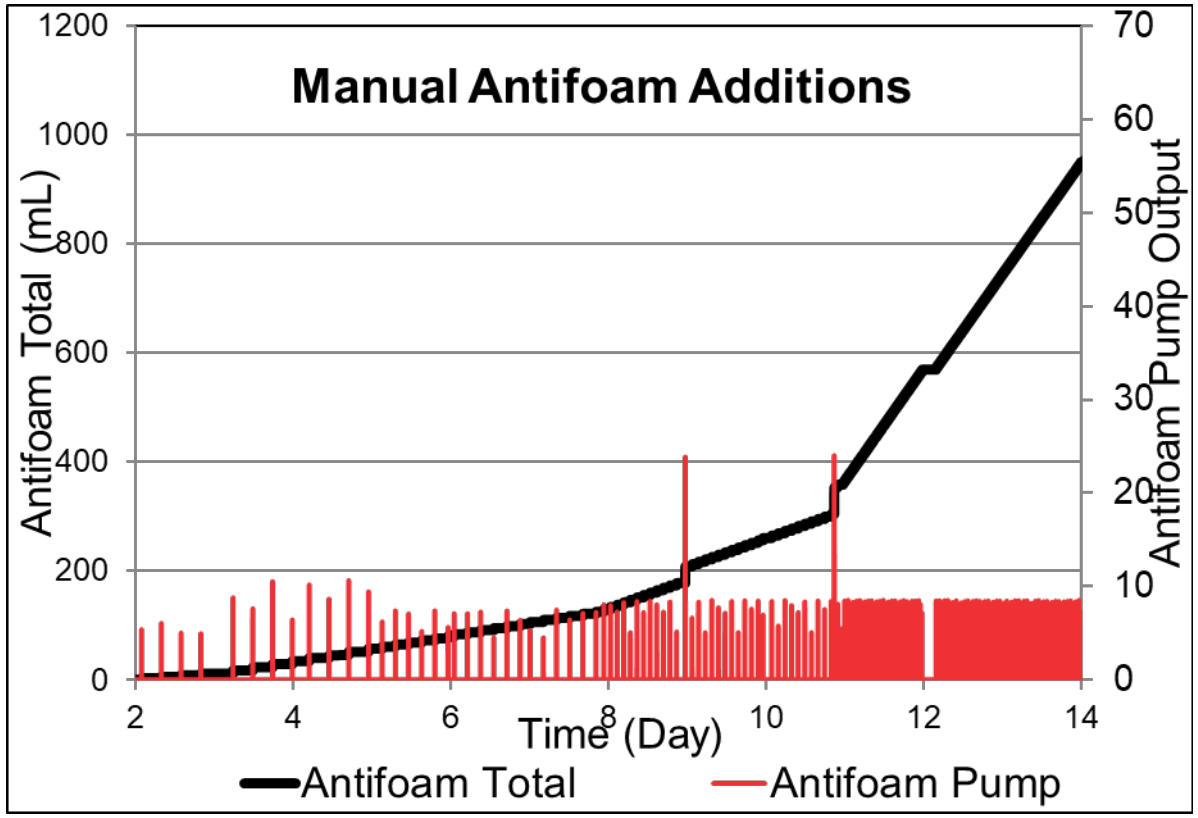


- The automated antifoam pumps turns on 138 times during the run, dispensing 3.8mL(on average) each time.



- Manual antifoam pump turns on 510 times, dispensing 1.87mL (on average) each time.
  - Approximately 25 mL added each time a foam out was observed





- The automated antifoam pumps turns on 138 times during the run, dispensing 3.8mL(on average) each time.

- Manual antifoam pump turns on 510 times, dispensing 1.87mL (on average) each time.
  - Approximately 25 mL added each time a foam out was observed

This data demonstrates a 47% reduction in the amount of antifoam used when the foam probe is employed.

Cell Culture Results

50 L S.U.B. Side-by-Side Fed Batch

Standard gassing strategy

50 L S.U.B. Perfusion

Aggressive perfusion application

50 L S.U.B. Side-by-Side Fed Batch

Aggressive gassing strategy

0.1 VVM total gas flow

1000 L S.U.B. Fed Batch

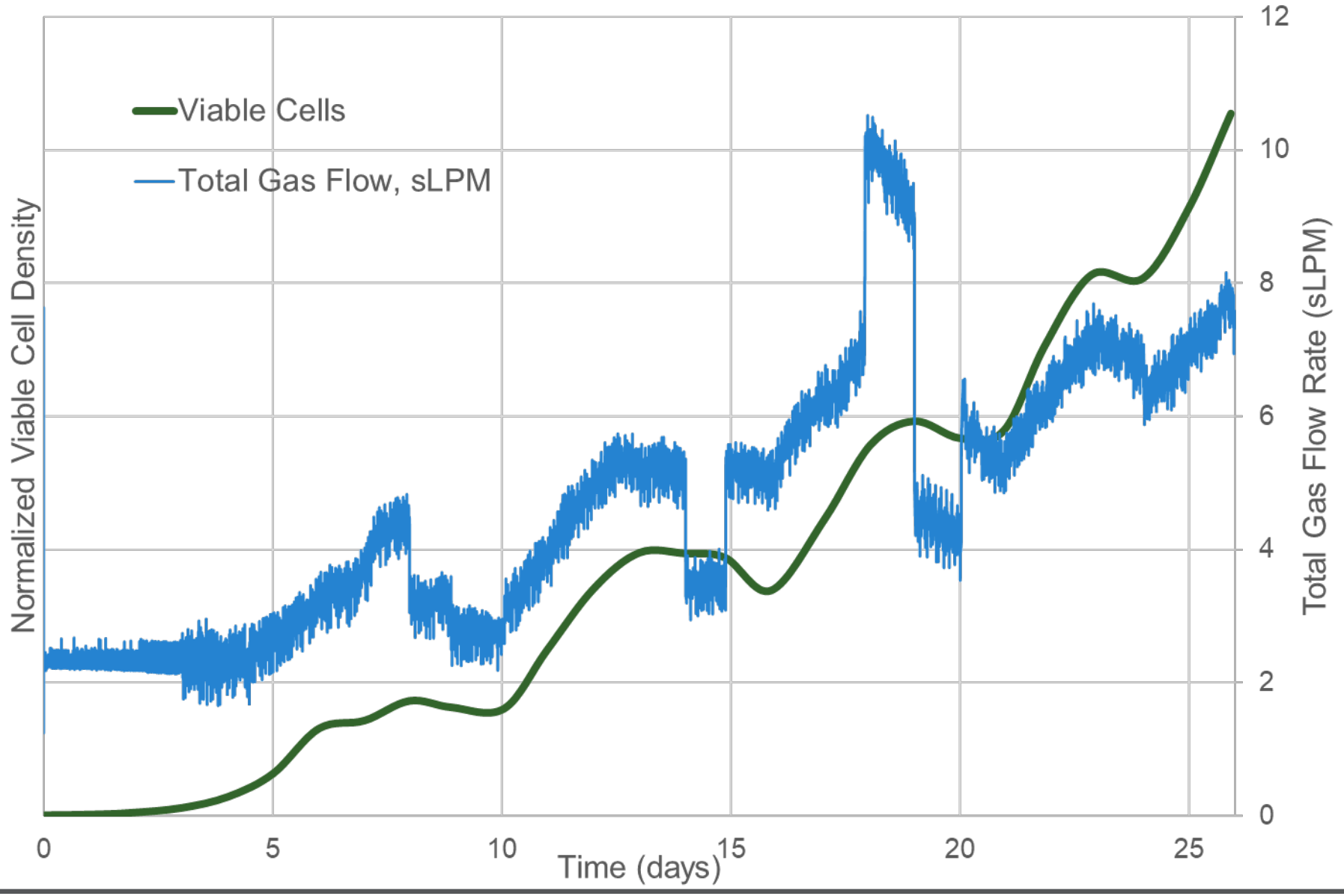
Aggressive gassing strategy

0.1 VVM total gas flow

Goal: Demonstrate scalability of the foam probe across multiple S.U.B. sizes and its application to aggressive processes

50 L SUB Perfusion Results

- Gassing Strategy
  - % DO, 30% setpoint
    - O2 flow rates allowed to vary based on the relationship between power input of the impeller and O2 demand by the cell culture.
  - pH D0-3, 7.2; D3-14 7.0
    - CO2 input
- Perfused with ATF
  - Automated bleed using biocapacitance probe



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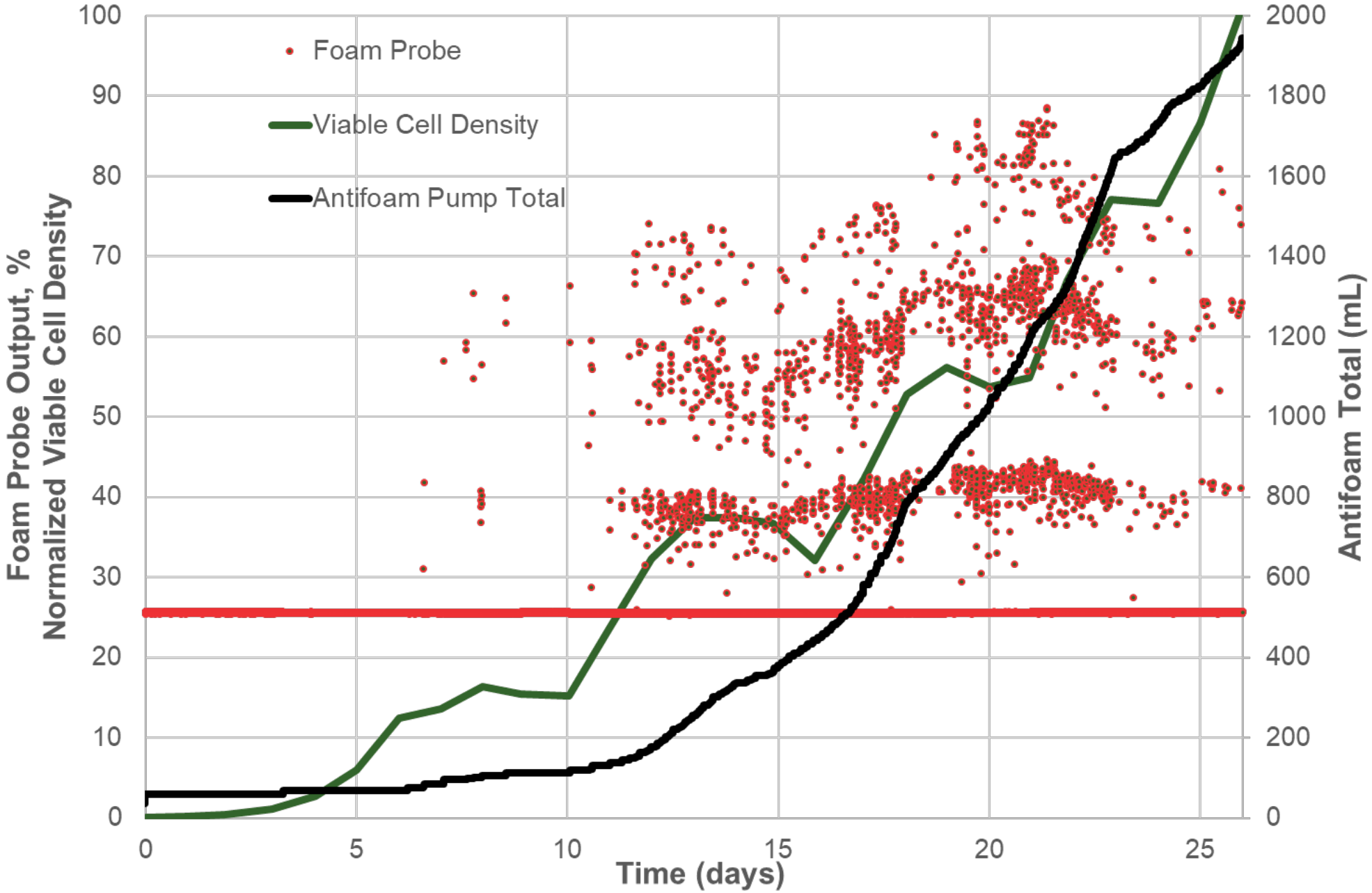

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Cell Culture Results

50 L S.U.B. Side-by-Side Fed Batch

Standard gassing strategy

50 L S.U.B. Perfusion

Aggressive perfusion application

50 L S.U.B. Side-by-Side Fed Batch

Aggressive gassing strategy

0.1 VVM total gas flow

1000 L S.U.B. Fed Batch

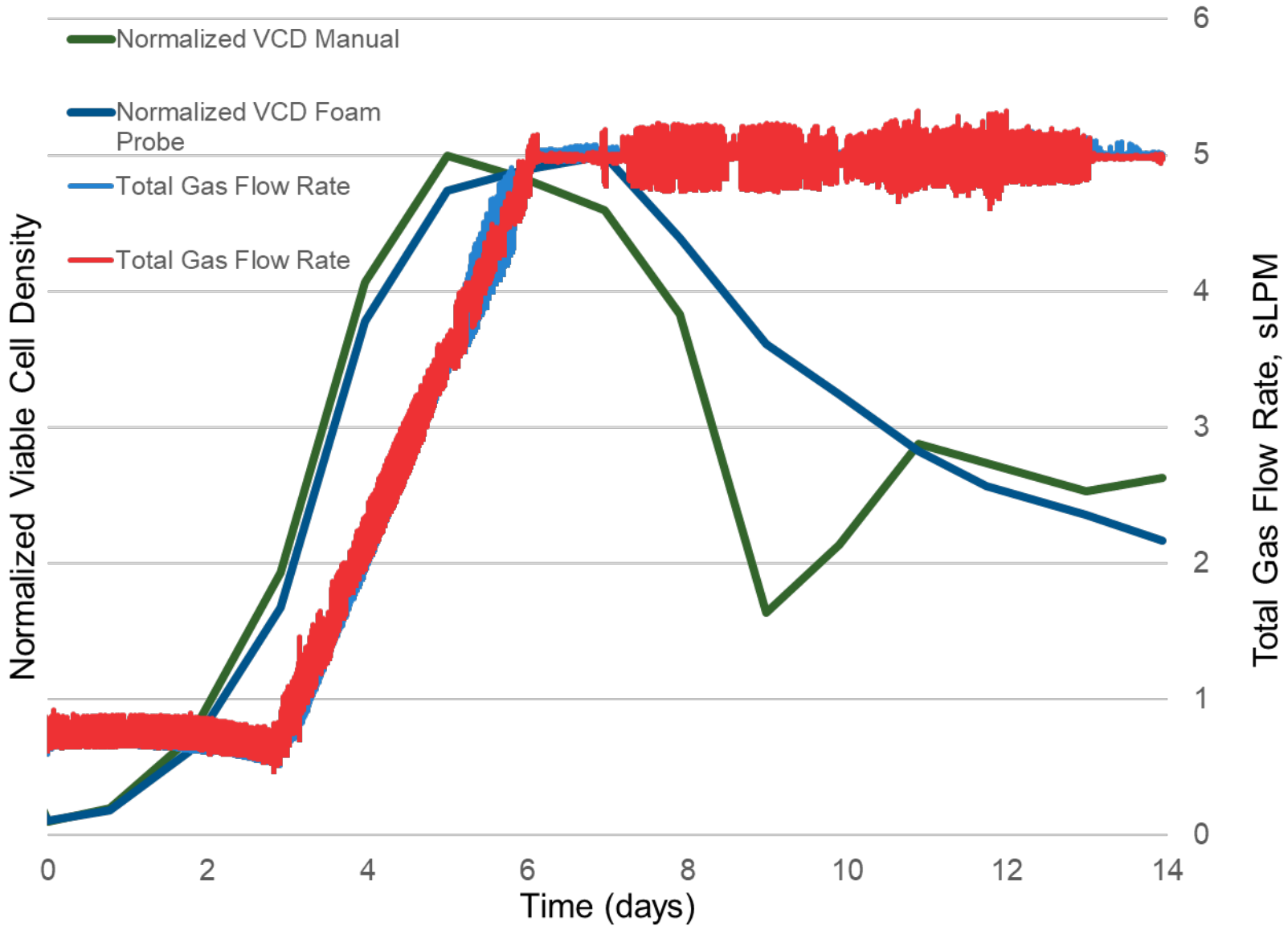
Aggressive gassing strategy

0.1 VVM total gas flow

Goal: Demonstrate scalability of the foam probe across multiple S.U.B. sizes and its application to aggressive processes

50 L SUB Side-by-Side Fed Batch, Aggressive Gassing

- Gassing strategy , DHS only
  - 30% DO
    - N2/O2 as needed to maintain setpoint
    - Air supplement to allow total gas flow to equals 0.1 VVM (5sLPM)
  - pH D0-3, 7.2; D3-14 7.0
    - CO2 input
- Foam Control
  - Controlled by foam probe
  - Manually controlled via automated dosing



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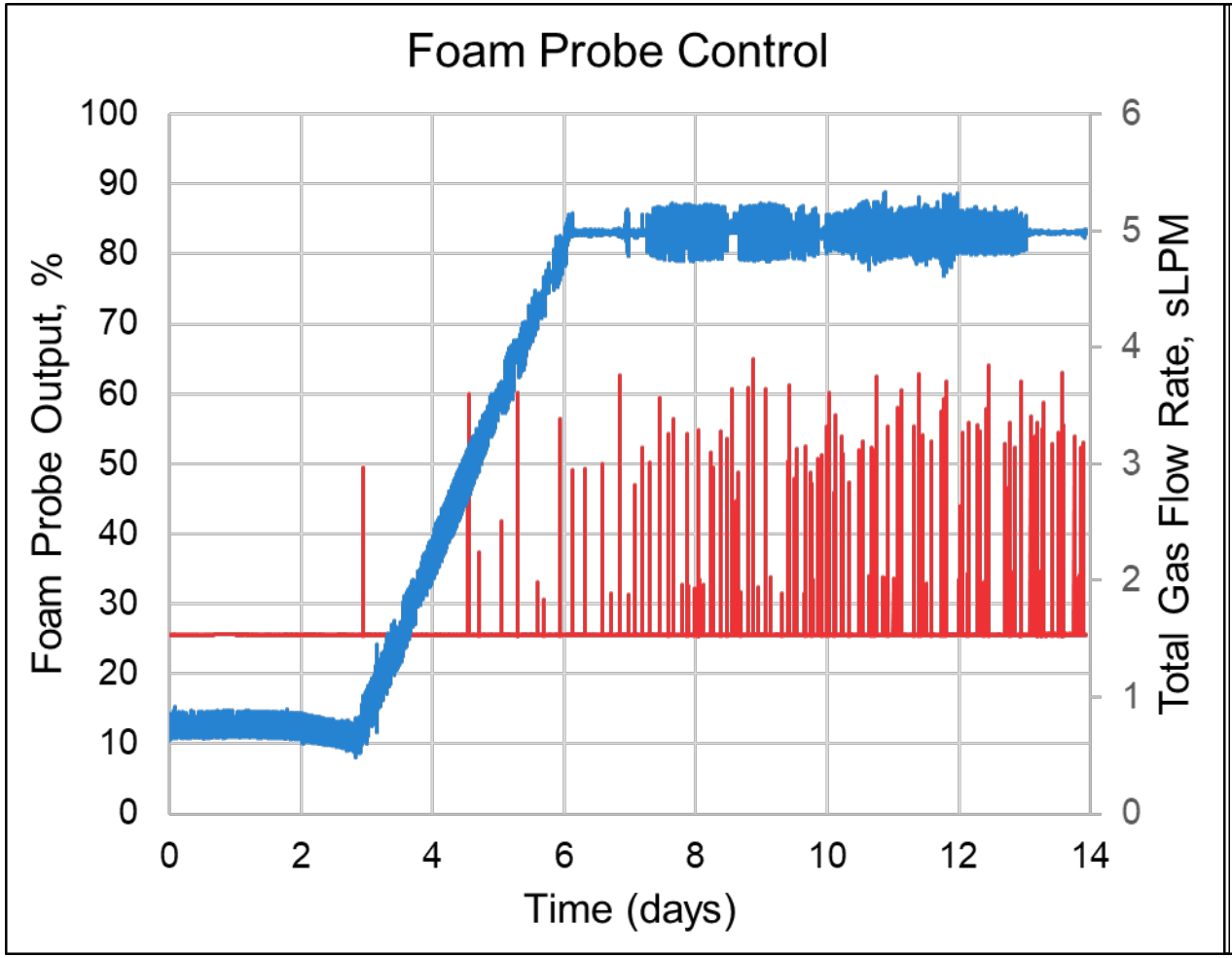
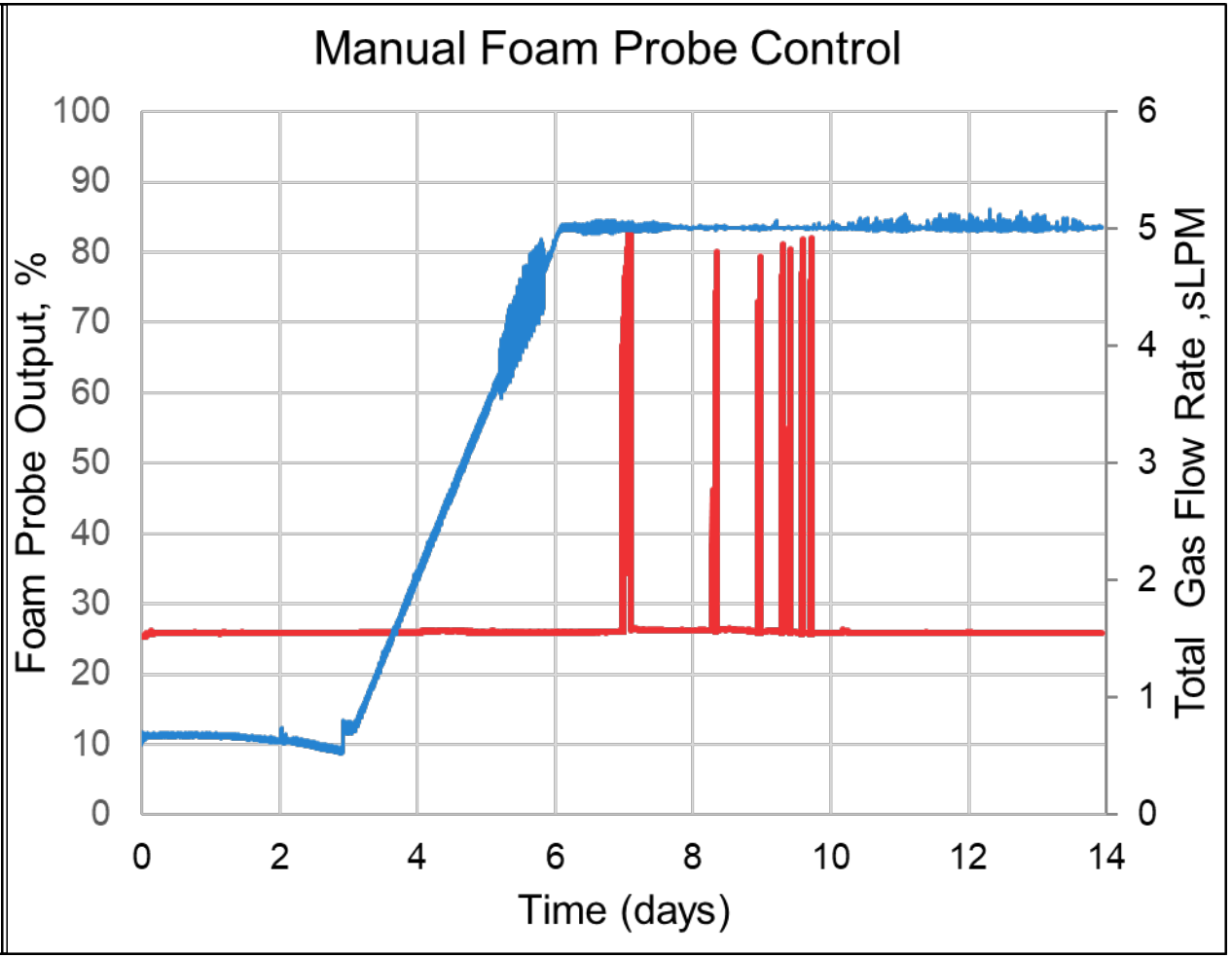
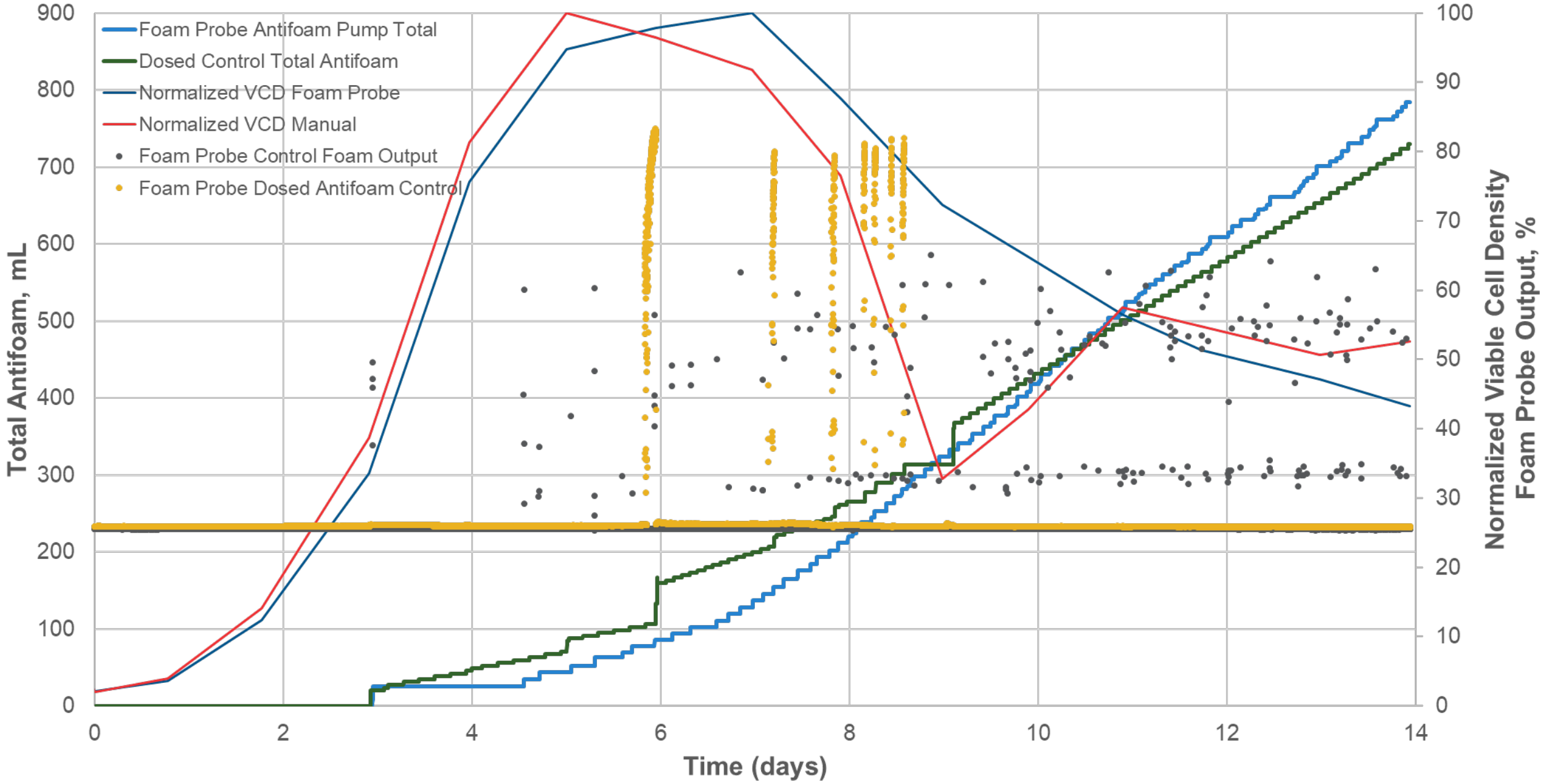




- Foam control equation:
  - When PV>**35** set pump output to **60** for **10**s then wait **30**s

- Manual dosed foam control, gradually increasing the dosing schedule as the culture progresses
- Back up foam control using the foam probe
  - When PV>**80** set pump output to **100** for **10**s then wait **30**s



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Cell Culture Results

50 L S.U.B. Side-by-Side Fed Batch

Standard gassing strategy

50 L S.U.B. Perfusion

Aggressive perfusion application

50 L S.U.B. Side-by-Side Fed Batch

Aggressive gassing strategy

0.1 VVM total gas flow

1000 L S.U.B. Fed Batch

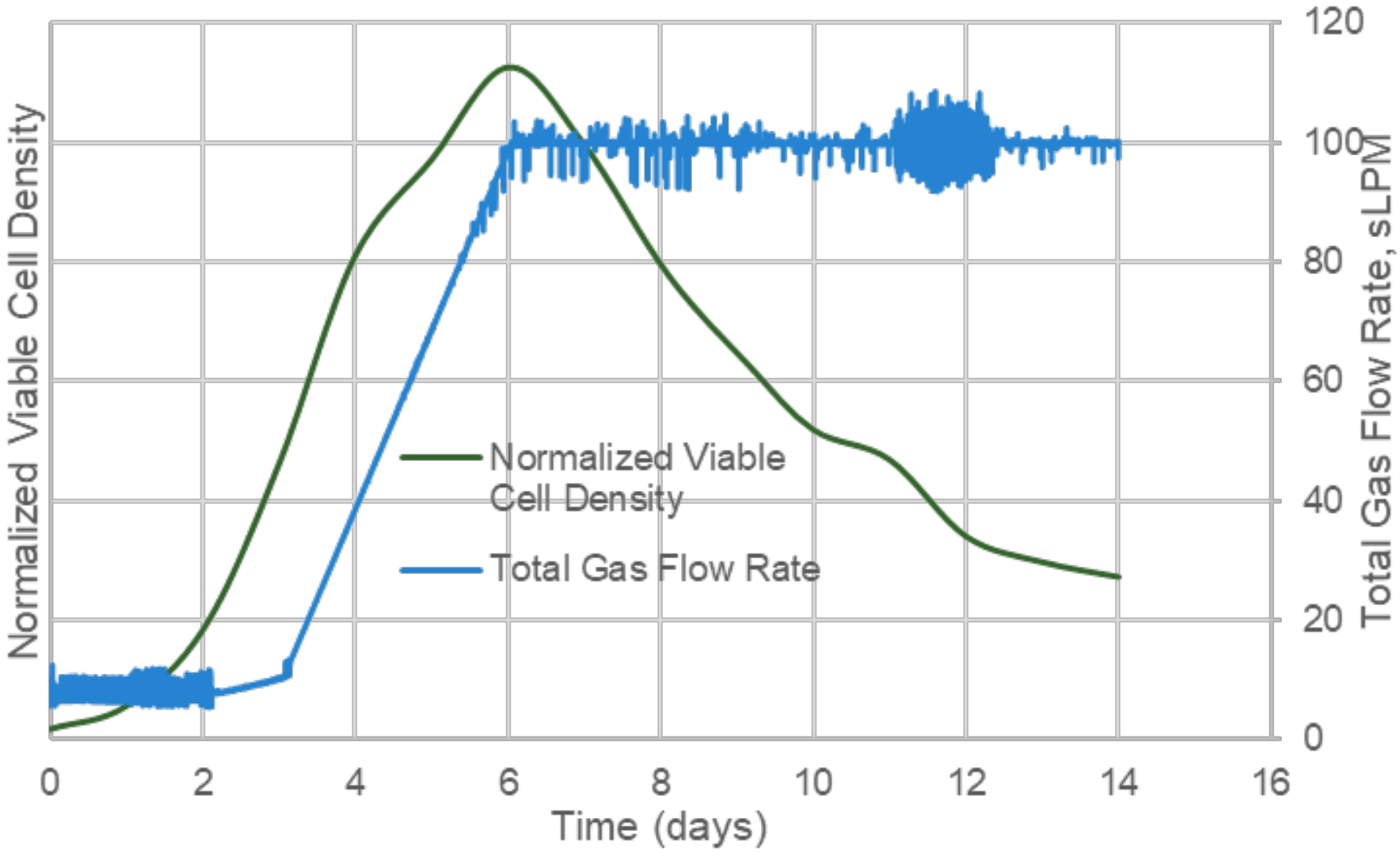
Aggressive gassing strategy

0.1 VVM total gas flow

Goal: Demonstrate scalability of the foam probe across multiple S.U.B. sizes and its application to aggressive processes

1000L S.U.B. Fed Batch Aggressive Gassing

- Gassing strategy , DHS only
  - 30% DO
    - N2/O2 as needed to maintain setpoint
    - Air supplement to allow total gas flow to equals 0.1 VVM (100sLPM)
  - pH D0-3, 7.2; D3-14 7.0
    - CO2 input
- Foam Control
  - When PV>**35** set pump output to **240** for **10**s then wait **30**s



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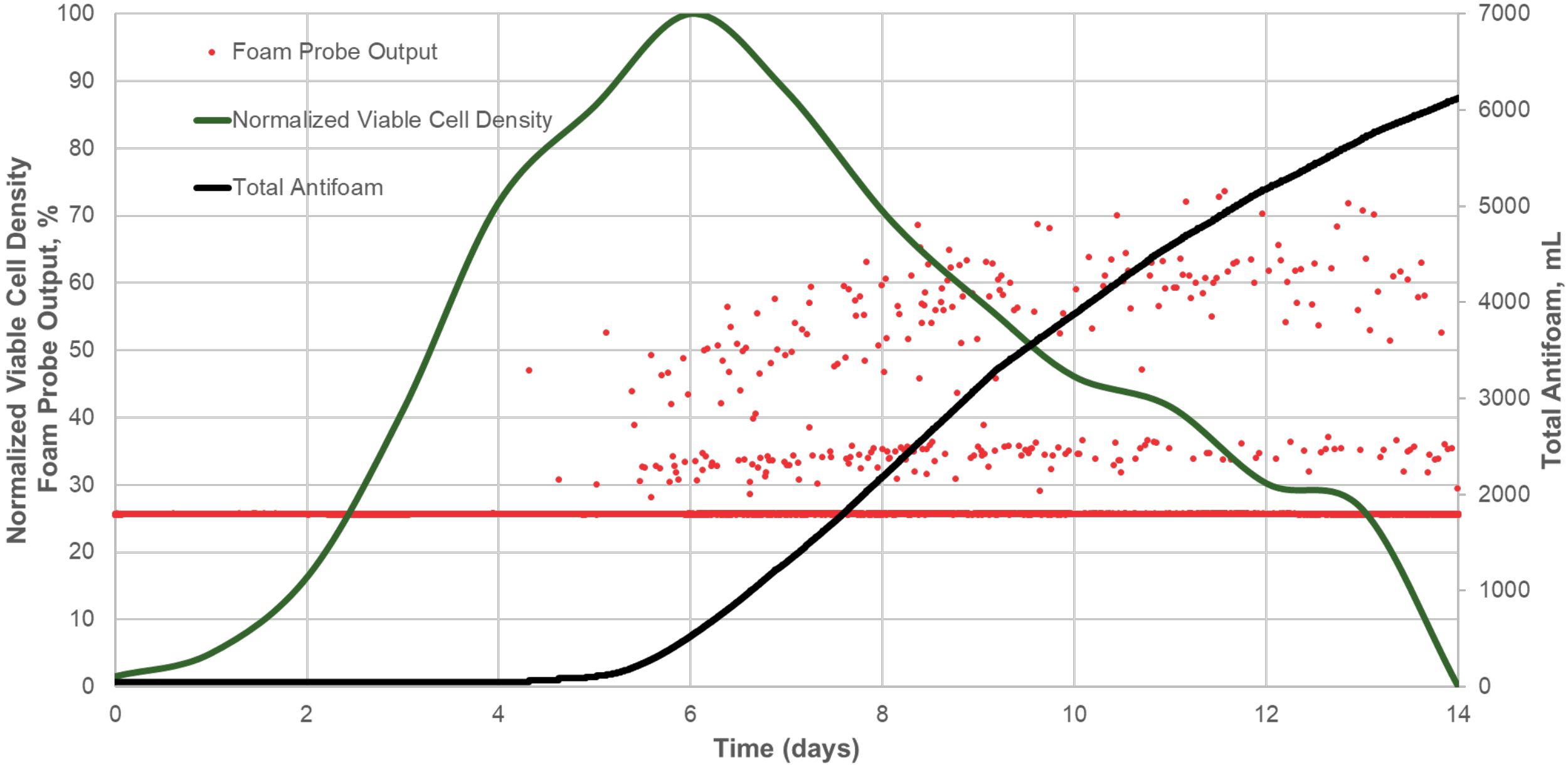

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Conclusion

50 L S.U.B. Side-by-Side Fed Batch

Standard gassing strategy

50 L S.U.B. Perfusion

Aggressive perfusion application

50 L S.U.B. Side-by-Side Fed Batch

Aggressive gassing strategy

0.1 VVM total gas flow

1000 L S.U.B. Fed Batch

Aggressive gassing strategy

0.1 VVM total gas flow

The single-use foam probe is a scalable solution for foam control in standard and aggressive cell culture processes

Conclusion

50 L S.U.B. Side-by-Side Fed Batch

Standard gassing strategy

50 L S.U.B. Perfusion

Aggressive perfusion application

50 L S.U.B. Side-by-Side Fed Batch

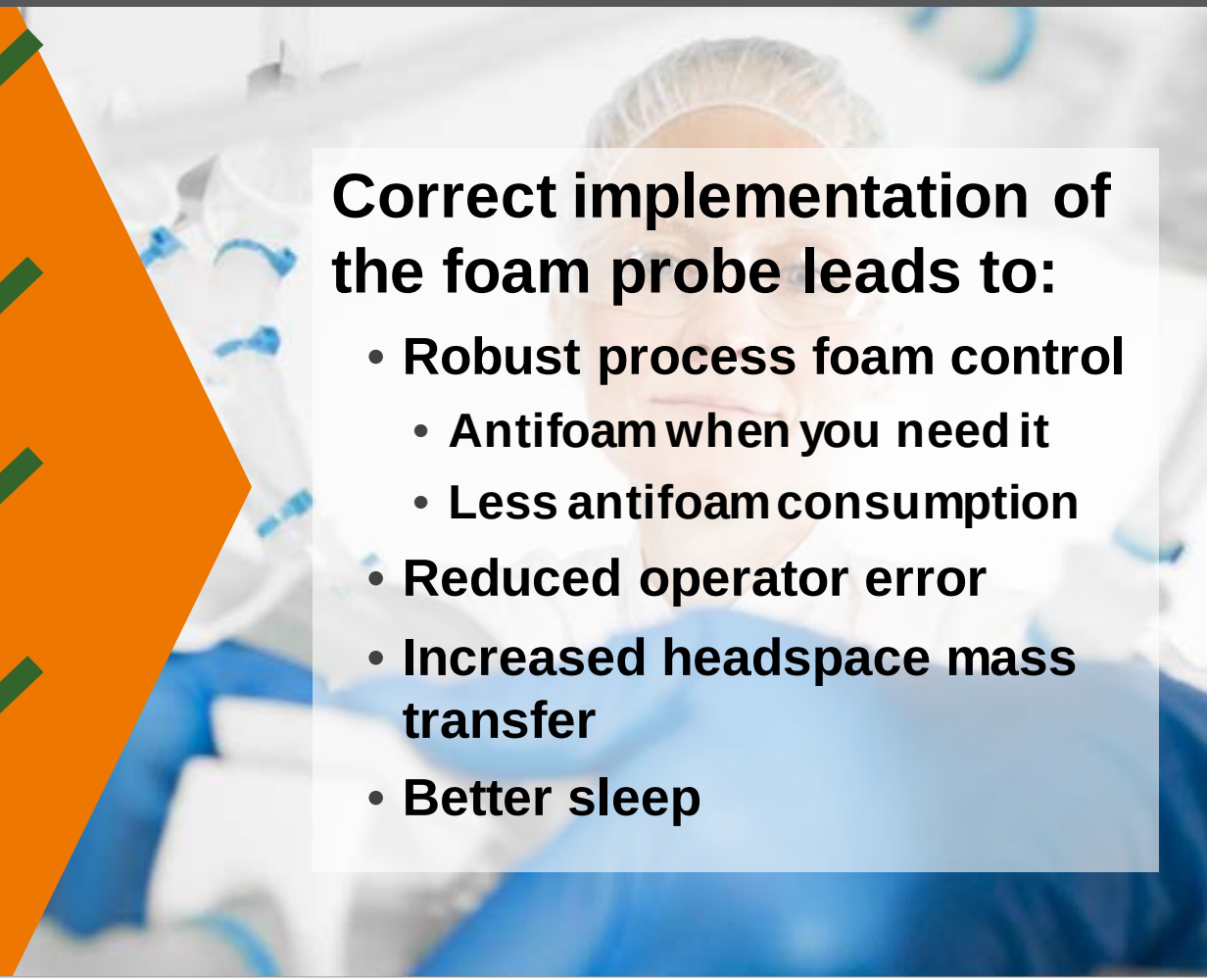
Aggressive gassing strategy

0.1 VVM total gas flow

1000 L S.U.B. Fed Batch

Aggressive gassing strategy

0.1 VVM total gas flow



Correct implementation of the foam probe leads to:

- **Robust process foam control**
  - **Antifoam when you need it**
  - **Less antifoam consumption**
- **Reduced operator error**
- **Increased headspace mass transfer**
- **Better sleep**

The single-use foam probe is a scalable solution for foam control in standard and aggressive cell culture processes

Acknowledgement

- R&D Advanced Technology and Process Development
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  - Saonearadei In

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