Real-Time, Non-Invasive Detection of Bioreactor Status and Contamination from Volatile Organic Compound (VOC) Gas Exhaust

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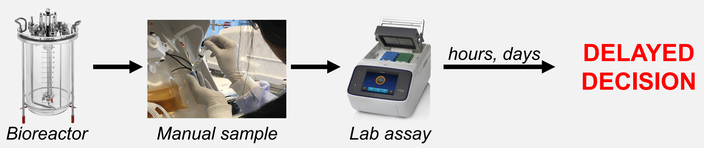
Current challenges in biomanufacturing

Traditional biomanufacturing relies on:

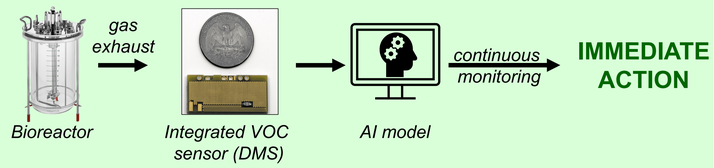
- Offline sampling
- Manual measurements
- Delayed contamination testing
- Batch failure discovered too late

Current bioreactor monitoring:



Technology solution:

Non-invasive VOC monitoring of gas exhaust:



- Bioreactor exhaust VOCs are endpoints of cellular metabolism
- VOCs provide a non-invasive view into culture health (status, expansion)
- Contaminants (bacteria, fungi) emit unique VOC signatures that can be utilized for screening
- Utilizes our DMS sensor, which measures individual VOC species (akin to chip-based mass spectrometry)

Why VOC monitoring is different

Real-time outputs include:

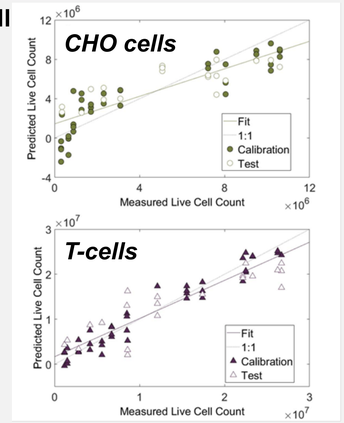
- Cell growth
- Contamination
- Process status
- Non-invasive (measuring gas exhaust)

Conventional PAT	VOC-based PAT
Operator intensive (manual)	Autonomous
Invasive	Non-invasive (gas exhaust)
Delayed	Near real time
Periodic	Continuous
Central laboratory processing	Integrated VOC sensor

VOCs are predictive of cellular growth [1,2]

Bioreactor VOCs correlate with cell density, providing a non-invasive means to assess growth state.

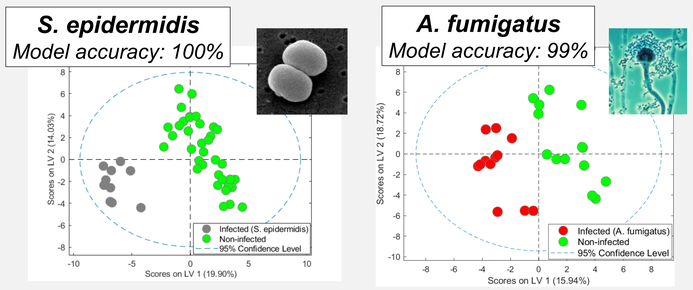
- Cellular VOC profiles change during expansion
- These changes can be measured in the gas exhaust (**non-invasive**)
- Predictive models estimate viable cell density
  - CHO: $R^2 = 0.67$
  - T-Cells: $R^2 = 0.77$



Bioreactor contamination detection [2,3,4]

Sensors detect contamination from ~10 CFU (colony forming units)

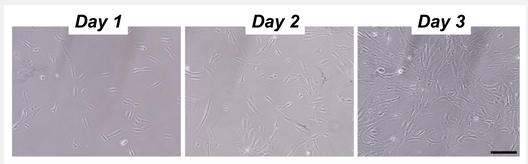
Contaminant	Studied species	Earliest timepoint of detection
Bacteria	*S. aureus* *P. aeruginosa* *B. subtilis*	2 hours post inoculation (10 CFU)
Fungi	*C. albicans* *A. brasiliensis*	6 hours post inoculation (10 CFU)
Mycoplasma	*M. arginini*	24 hours



Stem cell expansion monitoring [3,4]

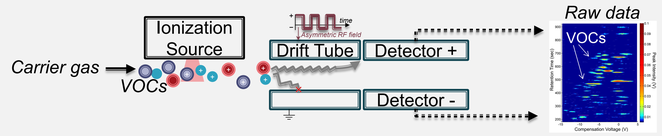
- Mesenchymal stromal cells (MSCs) studied
- VOC samples collected during expansion

Distinct VOCs increase and decrease as stem cell (MSC) cultures proliferate



Differential mobility spectrometry (DMS) [5]

- Original use: military explosives, chem warfare detection
- Our lab tailored sensors for bioreactor VOC detection
- Like mass spec, measures individual VOC species with sensitivities in the parts-per-trillion



DMS sensors can be combined with other components to improve VOC detection:

- Micro-Preconcentrators [6,7] (enhances VOC sensitivity)
- Micro GC columns (enhances VOC separation)

Military impact

Bioreactor operational benefits of VOC sensors

- Earlier contamination detection
- Reduced batch loss
- Continuous process awareness
- Reduced operator burden
- Improved manufacturing resilience
- Supports point-of-need biologics production
- Enables autonomous manufacturing

Development pathway

Completed:

- Studied CHO, primary T-cells, stem cells (MSCs), bone constructs
- VOCs correlate with expansion
- Detect bacterial, fungal, and mycoplasma contamination

Next:

- Sensor integration into closed-loop process control
- Study other cell and contaminant types

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Citations

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4. Linderholm A et al (2024) *Anal. Bioanal. Chem.*
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7. Chew BD et al (2024) *Anal. Chem.*

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