ENABLING BIOMANUFACTURING AND AUTOMATION THROUGH REAL-TIME SENSING OF pH AND DISSOLVED OXYGEN

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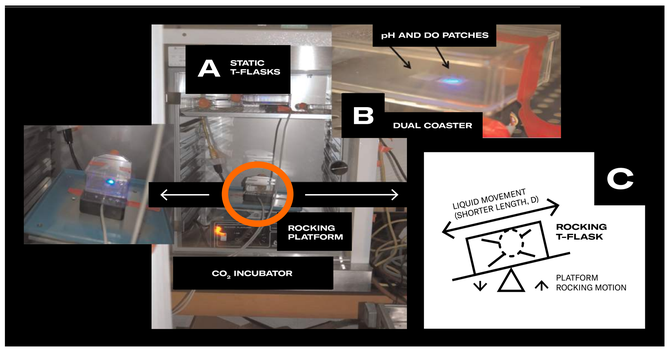
SCIENTIFIC BIOPROCESSING

A NEW APPROACH

A NEW APPROACH TO CELL CULTIVATION: OPTICAL SENSORS

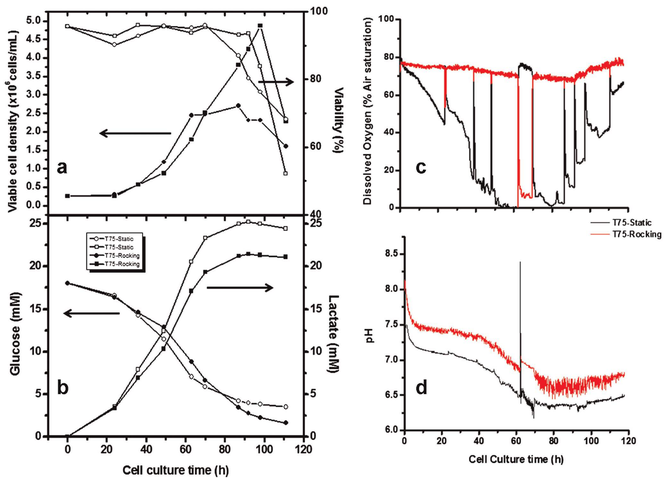
- The most commonly-used sensors in bioreactors are electrochemical probes but are unsuitable for T-flasks and microfluidics devices.
- Therefore researchers suffer from a lack of fundamental knowledge of the physical background and controlling parameters in early stage bioprocessing development.
- There is now an acute need for improvements. Real-time on-line monitoring of key parameters in bioprocessing scouting devices is needed to produce conditions representative of manufacturing.[1]

HYBRIDOMA CELL GROWTH STUDY IN ROCKING VS STATIC T-FLASKS



- Non-adherent SP2/0-based mouse hybridoma cells secreting IgG3
- T-75 flasks, static and on a rocker platform

Cell Culture Comparability Study Between Static and Rocking T75-flasks After Cell Vial Thaw



- Cell cultures grew faster and more densely in rocking than static t-flasks
- Rocking flasks yielded higher viable cell density (VCD) (1.8-fold increase) and 25% less lactate production compared to static flasks.
- DO in the rocking flask never dropped below 70% versus the static flask dropping to zero in two days leaving them anoxic for hours at a time.
- Agitation had a positive impact on maintaining physiological pH
- 31% higher antibody titer than static flasks
- Static T-flasks should be passaged by day 2 where rocking flasks never reached 0% DO and can be passaged by 3.5 days with cell viability profile remaining above 90%.
- Hypoxia can drive and maintain genetic instability, and hypoxic cells can acquire a mutator phenotype that consists of decreased DNA repair, an increased mutation rate and increased chromosomal instability.[2]
- Monitoring DO profile data may increase cell line genetic stability.[3]

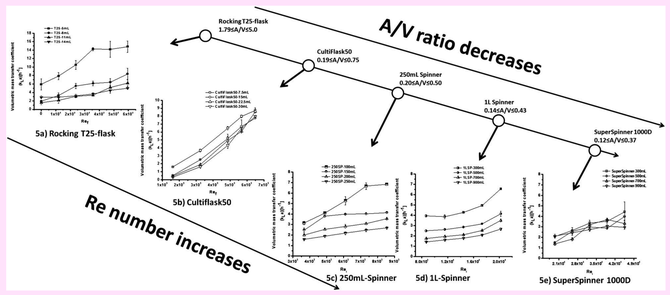
ID·SENSORS

SCALE DOWN STUDY

SBI's low cost, disposable DO and pH sensors in rocking T-flasks matching k_La with a 10L wave bioreactor[1]

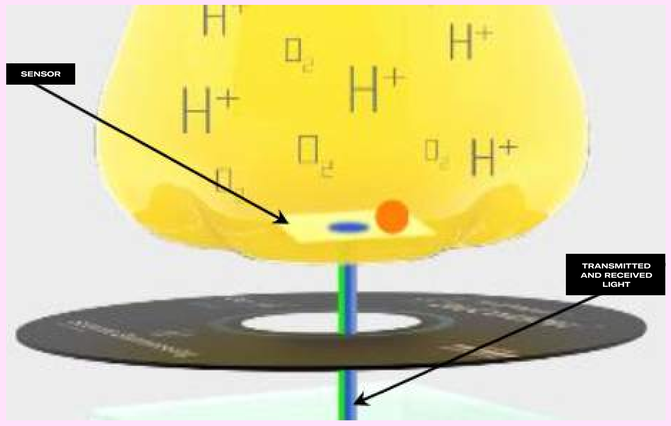
- Compared three T-flask geometries (T-25, T-75 and T-150) with optical ID·Sensors pH affixed to the flasks.
- Measured k_La of spinner flasks and found the T-flask superior.
- The ID·Sensor DO was used to accurately estimate the k_La in rocking T-flasks allowing researchers to match it to a Cultibag wave bioreactor.
- T-flasks have high surface area-to-volume ratio (A/V, cm^{-1}) one order of magnitude higher than other process scouting devices (PSDs) even at low Reynolds values. k_La increases as A/V increases.[1]
- Traditionally, this was thought to compensate for lack of agitation.
- Traditional wisdom has been shown to be incorrect.

k_La Comparability Between Rocking T25-flasks and Other Devices



- Rocking T-Flasks Have Superior Oxygen Transfer Capabilities Versus Other PSDs And Higher k_La At Lower Re Values.

OPTICAL SENSING



- Fluorescence-based technology
- Intelligent, dynamic (ID) products
- ID·Reader sits outside of culture vessel
- ID·Sensor is affixed inside of culture vessel
- Vessel wall must be transparent and transmit light >320nm

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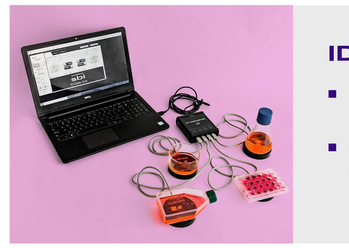
REAL TIME MONITORING

ID·READER AND ID·FIBER OPTIC READER



ID·DEVELOPER'S KIT

- Real-time, non-invasive monitoring in one kit
- Optical sensors for pH and dissolved oxygen (DO), readers and software

ID·ROCKER

Rocking and Instrumented T-Flasks are Better Flasks

- Adjustable T-flask rocking speed
- Closed loop control of rocking speed with feedback from the sensor measurements

ID·DATA HUB

Software for Optical Sensors

- Select the type of sensor you are using, pH or dissolved oxygen
- Select data collection mode
- Watch live data display
- Record data
- Single mode to capture single data points
- Scan mode to gather data at 10-second or higher intervals

CONCLUSION

Four features required to deliver the power to optimize cell culture:

1. Reliable sensors for real-time monitoring from smallest to largest vessel
2. Automatic with control and closed loop feedback
3. Relevant physiological parameters at the cellular level
4. Economically remarkable and easy to demonstrate ROI

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