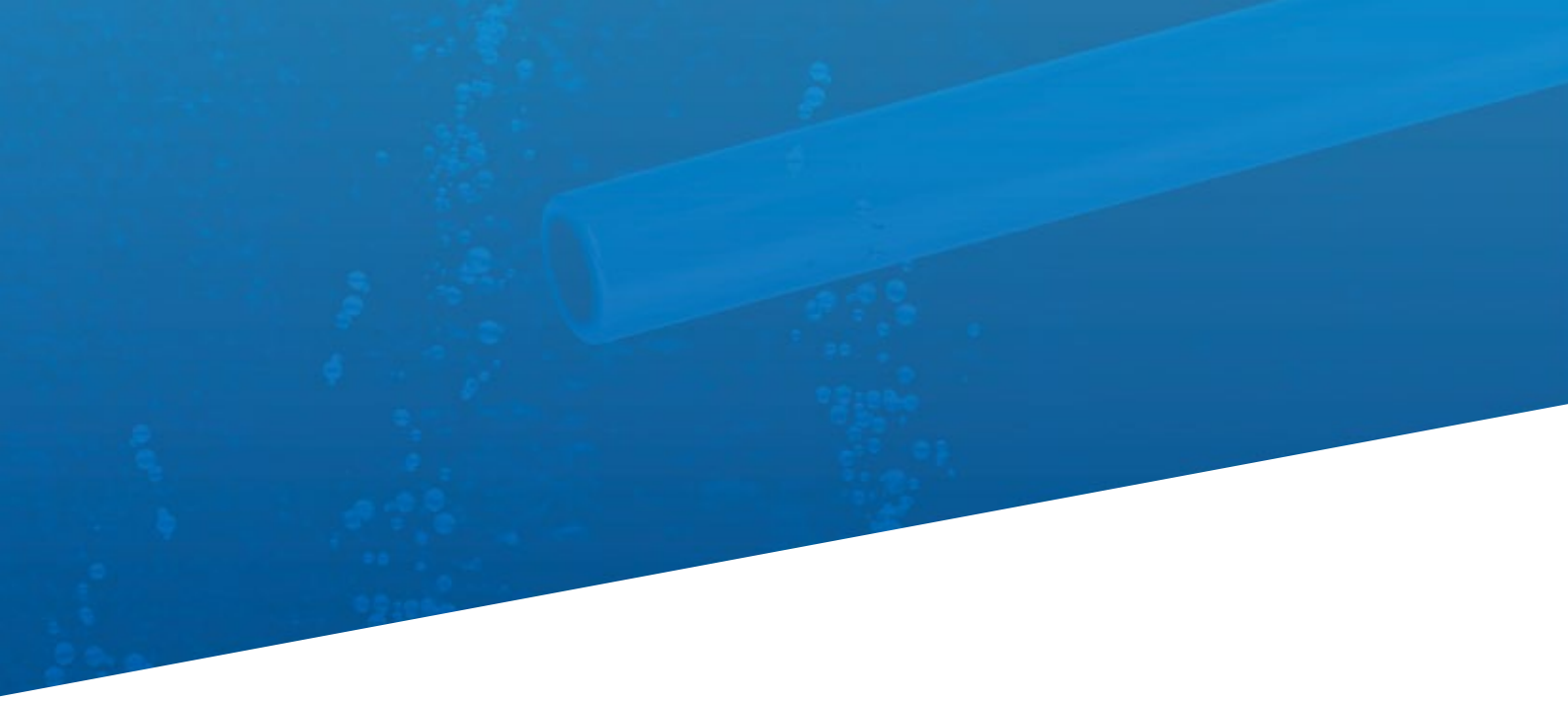
HAMILTON

Measurement Challenges with Optical Dissolved Oxygen Sensors

White Paper



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Abstract

Measurement of dissolved oxygen (DO) has long been known as a critical control parameter for optimizing cell growth in bioprocesses. Much has been written about different strategies for proper DO control. However, little information has been publicly available regarding optimization of the actual measurement accuracy and reducing common sources of process-related error. This paper aims to divulge these details for the first time. Specific consideration will be given to optical dissolved oxygen measurement which has become the predominant measurement technology in bioprocesses.

Introduction: Hamilton's Unique Perspective

Biopharma is a unique industry with equally unique requirements and challenges. For the past 30 years, Hamilton has focused Process Analytics research and development on overcoming these needs and hurdles, to grow a product offering specially designed for biopharma applications. Working closely with end users elucidated temperature, sterility, and hygienic requirements as three prime examples of necessary considerations for implementation in the bioreactor. Hamilton also partners closely with bioreactor manufacturers to ensure that sensors designed for biopharma are easily integrated into existing reactors as well as into future designs for minimal hassle at the end user site. Each sensor innovation was born from close customer collaboration with the goal of eliminating any process challenges they face.

The sensor must measure oxygen reliably and maintain suitable accuracy for dissolved oxygen (DO) control, despite repeated sterilization cycles. Hamilton's history of DO sensor development began with sterilizable polarographic DO sensors. However, polarographic sensors are based on electrochemical principles and thus require on-going maintenance of the electrolyte, membrane, and anode/cathode assembly. The electrochemical sensors are more susceptible to process variables such as carbon dioxide fouling, flow, and pressure variations. In an effort to substantially reduce these maintenance efforts and process effects, Hamilton introduced the first optical DO (oDO) sensors designed for the bioreactor.

The launch of a 12 mm hygienic, optical DO (oDO) sensor by Hamilton in 2007 eliminated reliance on electrochemical principles, so there is no need for a membrane, electrolyte, or anode/cathode assembly or the associated maintenance. These advantages, combined with digital sensor technology and output signals that mimic polarographic sensors, have allowed widespread adoption of Hamilton optical sensors in biopharma applications. Nevertheless, optical technology has its own application considerations that should be reviewed to ensure a successful measurement.

Process and Reactor Considerations

Hamilton's history with DO measurement and their interactions with biopharma customers and bioreactor manufacturers have revealed that bioreactor design can play a large role in successful oxygen measurement and control. DO is a critical control parameter for cell growth in bioreactor applications, so all factors that affect DO and DO measurement should be optimized for enhanced process performance.

Proper DO measurement and control is used to optimize OTR (Oxygen Transfer Rate) from gas to liquid phase and OUR (Oxygen Uptake Rate) of the cells by measuring dissolved oxygen in the liquid phase (see Figure 1). This amount of oxygen is also known as the degree of aeration. If oxygen levels drop below a determined setpoint, then cells can be stressed to the point of limited growth (hypoxia) or possibly cell death (anoxia). High levels of dissolved oxygen (hyperoxia) are undesirable due to oxygen toxicity. Too much gas (oxygen or air) can also cause excessive foam build-up that increases operational costs for chemicals (anti-foam) and equipment usage. Depending on the cell type, typical DO control is optimized at 30 to 60% air saturation with control limits of +10% and -5%. Different cell types (e.g. mammalian vs. bacterial) tend to have greatly varied OUR values. This value needs to be determined for each process to accurately determine oxygen control needs.

For most bioreactors, parameters that affect aeration are controlled through variations of traditional PID algorithms. The DO sensor measurement is the primary feedback mechanism for any changes to the control variables. For this reason, sensor accuracy and repeatability are critical for control. The ideal level of aeration as well as sensor mounting, reactor settings, and scale-up need to be evaluated for each process.

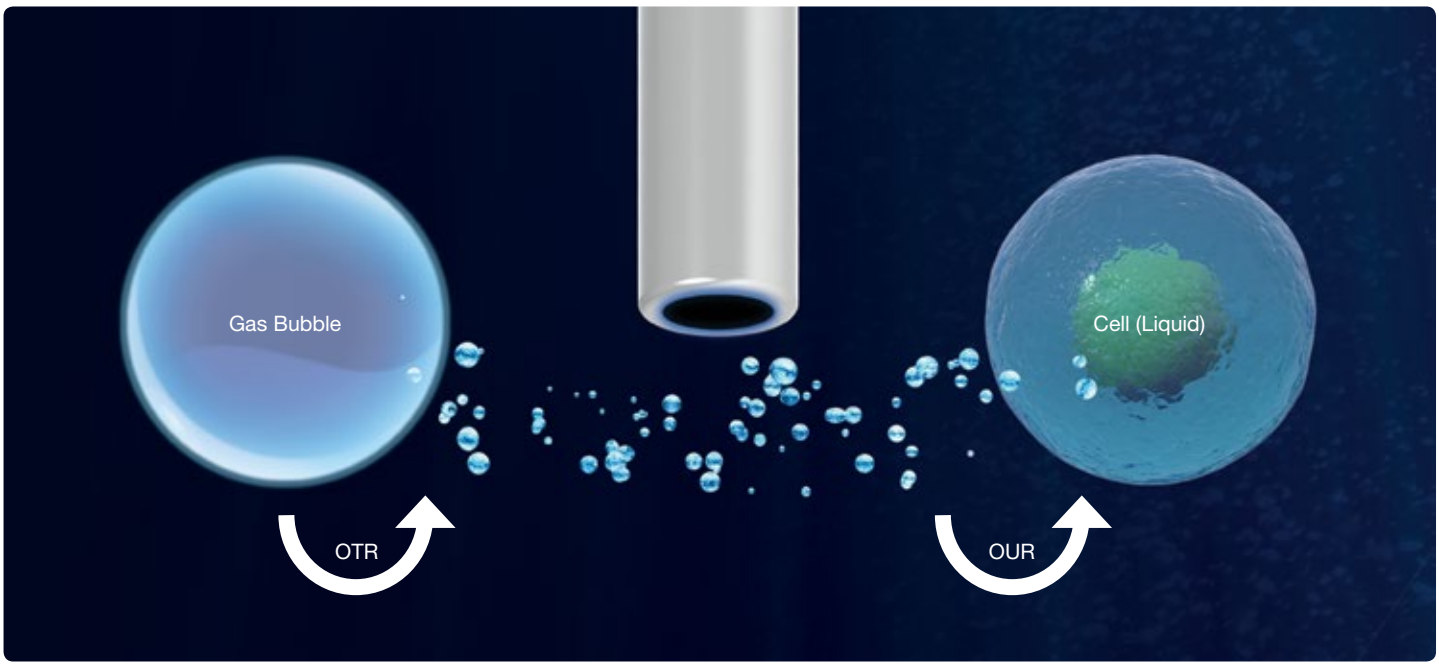


Figure 1: Oxygen must transfer from gas phase to liquid phase (OTR—Oxygen Transfer Rate) in order to be consumed by the cell (OUR—Oxygen Uptake Rate).

Process and Reactor Considerations (Cont.)

Figure 2 illustrates a typical bioreactor layout.

Sparger Design

Bioreactor manufacturers design the sparger to control the size of air bubbles for optimal OTR. The location of the sparger within the bioreactor with relation to the DO sensor must also be considered. Placing a sensor too close to the sparger may lead to inaccurate measurement due to the accumulation of bubbles and interference of gas phase oxygen. However, with a position too far from the sparger, the sensor reading could be non-representative of the entire bioreactor, due to stratification of DO in large reactors.

Gas Flow Rate

Gas flow entering the bioreactor is controlled by a mass flow controller. Flow rates are generally held to a specific setpoint while stirrer speed is adjusted for fermentation. For cell culture, flow rate has to be adjusted while stirrer speed is kept constant. Compliance with the setpoint is determined through DO measurement, so the precision and accuracy of the sensor are important for proper flow.

Stirrer

The stirrer speed directly influences the OTR in that a faster stirring speed increases OTR. While a high OTR is desirable, rapid stirring can cause mechanical cell damage and excessive foam build-up. A vortex effect may occur where a pocket of air forms down the middle of the bioreactor and limits the effectiveness of the stirrer. However, lowering the speed too much can cause sedimentation and incomplete mixing, resulting in improper chemical feed control. There are many different designs of stirrers for different processes to optimize power input, bubble accumulation, and OTR for the given bioreactor shape; therefore, the stirrer design and settings should be optimized for every process.

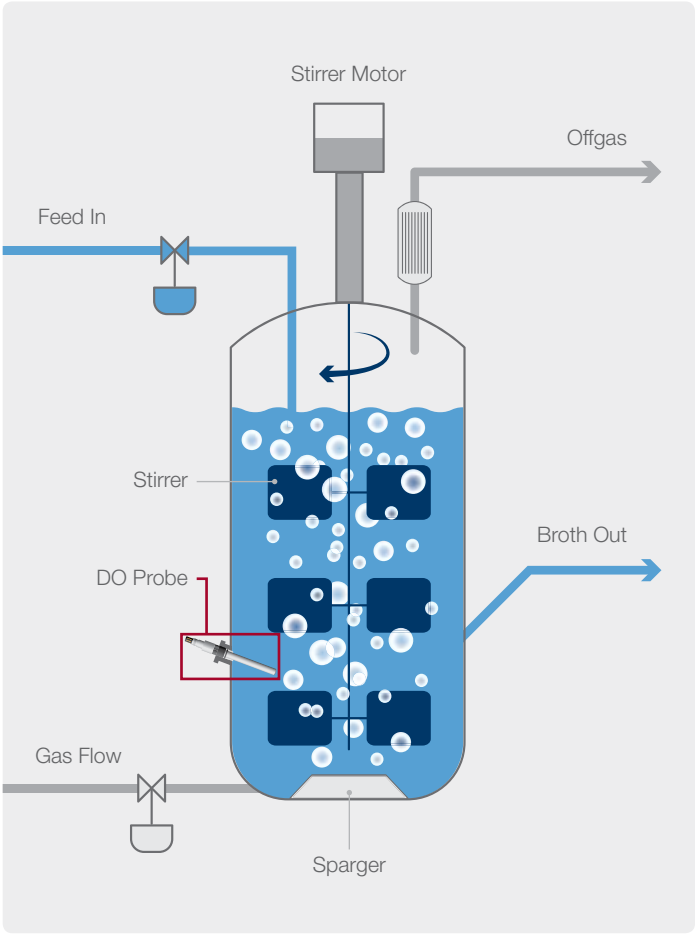


Figure 2. A basic bioreactor layout.

Scale Up

Scale-up is a term referring to the transfer of the fermentation process from the R&D stage to the pilot or production stage. The same control parameters are still required; however, the bioreactor design is often much different than typically found in the laboratory. The larger bioreactor volume resulting from scale-up slows down the OTR, further resulting in slower DO detection. If the PID control algorithms are set for the smaller scale, the response will be inaccurate. The mass transfer coefficient for oxygen, kLa, must be kept constant in the scale up process to accurately predict OTR and OUR values. Frequent test runs need to be performed to adjust the control algorithms for dissolved oxygen.

Physical aspects of the bioreactor such as the sparger locations, stirrers, and sensor mounting points are also affected by scale-up. The process connection for the sensor are often different, thus armature and insertion depth may need to change. If the sensor is inserted horizontally into the vessel, then the length of the sensor and related armature must be enough to get the sensor fully into turbulent flow within the vessel.

Sensor Mounting

With any sensor installation, the mounting of the DO sensor should be reviewed (see Figure 3 and 4).

Sensor Depth

For vertical headplate installations, the sensor should extend well into the vessel to avoid exposure to air if liquid levels drop below the sensor tip. For side-mount installations, the tip of the DO sensor should extend past the inner wall of the bioreactor at least 10 mm. This length ensures homogeneous flow and quick response to changes in oxygen levels. Flush or recessed sensor installations should be avoided as they are more prone to coating issues, may have slower response, and have possible sanitary concerns.

Sensor Angle

For side mounted sensor installations, it is common that angled sockets are used. The angle is desirable for polarographic sensors as gravity keeps the electrolyte at the membrane tip. Angled mounting is not a requirement for optical DO sensors; however, the self draining aspect of the angled socket may be desirable for sanitary reasons. Hamilton recommends a 15 degree angle over horizontal for best drainage of any dead space.

Bubbles

Air bubble build-up on the sensor tip can be a source of signal instability (noisy signal). This can often be correlated with sensor distance from the stirrer, stratification within the vessel, and stirrer speed. As a general guideline, position the sensor away from the sparger to avoid air bubbles adhering to the sensor tip. This can be accomplished by choosing the right process armature and sensor length. Positioning the sensor near the stirrer can also help to remove bubbles from the sensor tip.

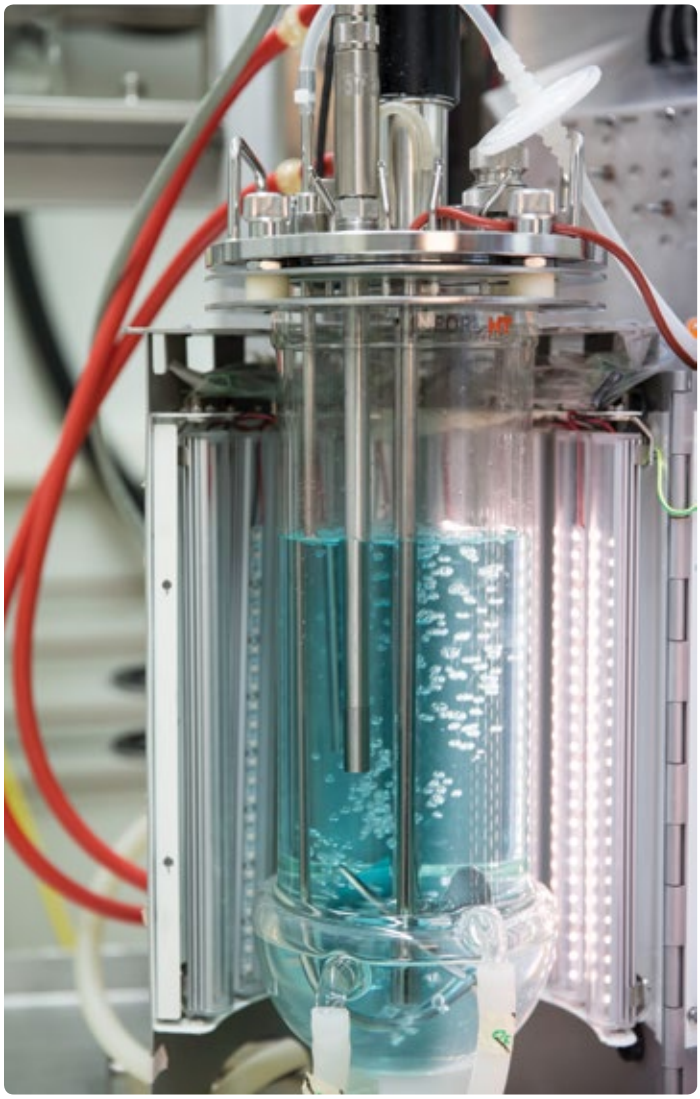


Figure 3. Small benchtop bioreactors rely on vertical sensor mounting.

Figure 4. DO and pH sensors are often inserted in the side of production-scale bioreactors.

Optimized Measurement Accuracy

Like most analytical measurements, current DO sensors require frequent calibration to maintain accuracy. Historically, polarographic sensors have exhibited measurement changes due to degradation or poisoning of the electrolyte and aging of the anode/cathode assembly. These issues have driven users to create calibration and verification procedures to check the polarographic sensor every run. Current oDO sensors are not immune to drift either. They may exhibit error due to changes in the luminophore from photobleaching, chemical attack, and repeated exposure to high temperature. The need for calibration has not vanished. What is often overlooked is compensation for external influences like temperature, pressure, and humidity during the calibration procedure.

Calibration Errors

Proper calibration plays an important role in maximizing measurement accuracy. Calibration in air within a laboratory environment may lead to potential errors if not compensating for atmospheric pressure and humidity changes. Ignoring these two variables may lead to maximum potential error of up to 13.2% for air calibration. For the zero point calibration, these errors disappear since there is no oxygen present in the calibration gas; nevertheless, temperature is still a factor. Temperature is compensated within the sensor; however, errors up to 3% can be seen if rapid changes in temperature occur. Ultimately, the temperature reading should be stable prior to calibration.

When a new sensor is to be calibrated (or new optical DO cap is installed), a two point calibration in air and nitrogen should always be performed. To get the best zero point calibration, high purity N5 nitrogen (99.999%) is required. The sensor should be mounted into a calibration fixture which allows free flow of the calibration gas with no back pressure or potentials for leaks (Figure 6). Nitrogen should flow past the sensor for at least 3 minutes to ensure that any residual oxygen is purged from the calibration chamber. A constant flow rate past the sensor should be maintained.

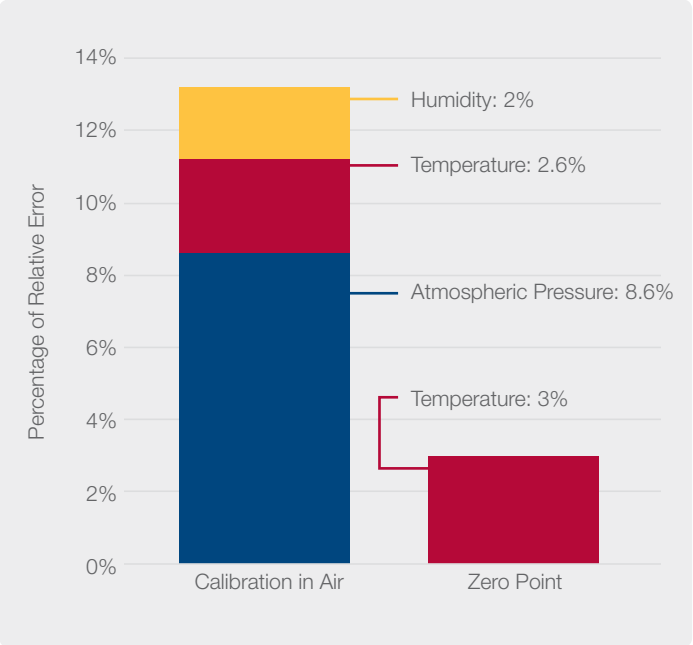


Figure 5. Up to 13.2% relative error can be found at the time of verification. Temperature, relative humidity at room temperature, and atmospheric pressure can all contribute to this error.

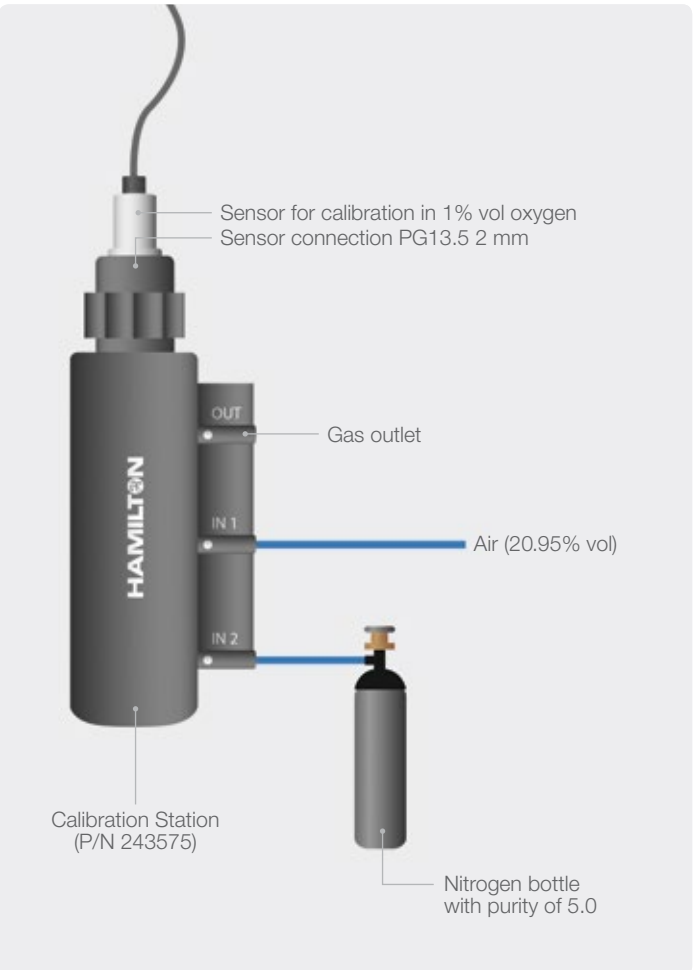


Figure 6. An example of a calibration station for use in working with DO sensors.

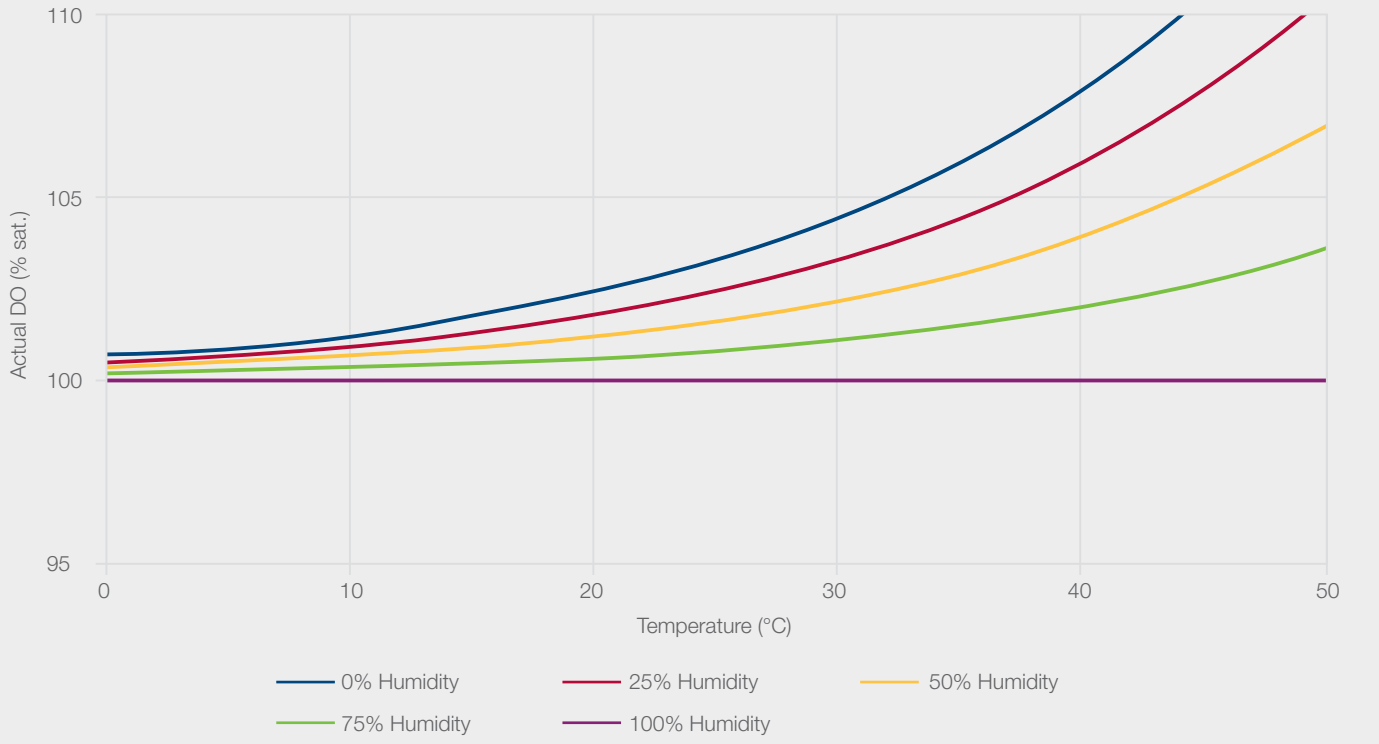
Calibration Errors (Cont.)

Effect of Atmospheric Pressure

Atmospheric pressure, also called barometric pressure, is the pressure within the earth's atmosphere. Standard atmospheric pressure at sea level is defined as 1,013.25 mbar (101,325 Pa). Atmospheric pressure varies widely on earth, depending on variables such as weather, climate, and altitude. Optical dissolved oxygen sensor measurements are based on the partial pressure of oxygen. The total pressure of a gas mixture is the sum of the partial pressures of each individual gas (Dalton's Law). This means that the partial pressure of oxygen is proportionally affected by the atmospheric pressure and during calibration this effect must be accounted for within the sensor in order to reduce potential error.

Effect of Humidity

Humidity has a direct influence on measurements of the oxygen concentration in the gas phase, as in calibration. In the liquid phase, there is no such effect, as liquids have a humidity level of 100%. In gas phase, decreasing humidity leads to an increase in oxygen concentration. Increasing temperature amplifies this effect as the gas has greater capacity to absorb both water vapor as well as oxygen.



Example: If the optical DO sensor is exposed to air at 40°C in 50% humidity the correct oxygen concentration is 103.9% sat. and not 100% sat., resulting in an error of almost 4%, so humidity must be properly compensated for.

Figure 7. Dissolved oxygen saturation increases with decreasing humidity. The effect becomes more prominent at higher temperatures.

Hamilton's optical DO sensors are based on oxygen concentration measurements in fully air saturated water. This requires proper laboratory calibration in air to be performed at the same 100% humidity level. Mounting the sensor over a beaker of water or wrapping the tip in a moist rag simulates the desired humidity level.

Calibration Errors (Cont.)

Effect of Temperature

Since temperature influences the activity of gas molecules and the partial pressure they exert on the sensing element of an oDO sensor, it must be measured and compensated for during calibration. The inherent design of oDO sensors includes an imbedded temperature element within the metal body of the sensor. Temperature differences between the temperature element inside the sensor and the ambient air could add up to 3% error. This error can be compounded by excessive handling of the sensor prior to or during calibration (see Figure 8). Body heat transfers through the metal sensor body and thereby increases the temperature beyond the reading of the room alone. During normal measurement in liquids, this temperature difference is not an issue due to the more efficient heat transfer properties of liquids than gases.

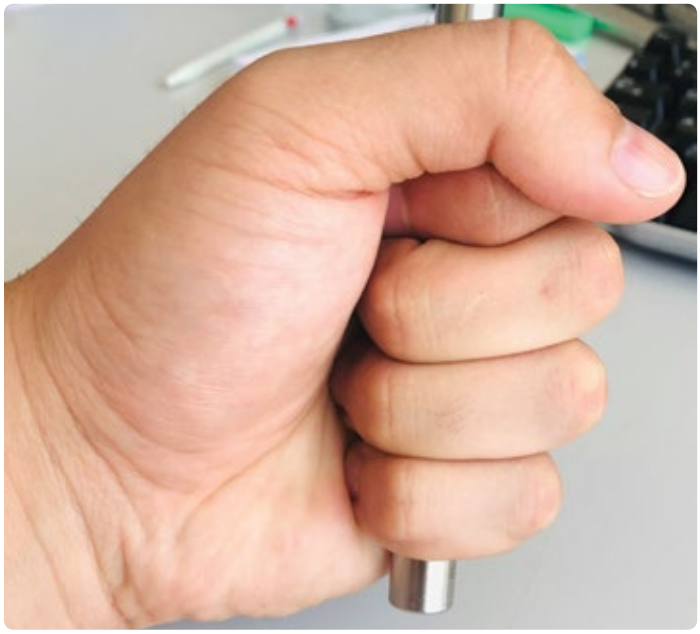


Figure 8. Body heat absorbed during handling of the sensor can cause calibration errors.

Challenges in Product Calibration

Many users deal with inaccuracy of the initial calibration and CIP/SIP effects by performing a product calibration. The typical procedure is to fill the bioreactor with liquid and sparge air over time until a value close to 100% air saturation in liquid is reached. At this point, a product (or process) calibration is performed to offset the initial calibration.

The effort to achieve full saturation for a product calibration can be time consuming. Often, full media saturation is not reached due to time constraints and issues of the solubility of oxygen in water that may have additional dissolved components. Additionally, this offset correction value works well at 100% saturation, but most biological processes are regulated at 30 to 60% sat. The outputs of optical DO sensors are based on the Stern-Volmer equation, thus are non-linear. Applying the same offset value from the product calibration (performed at 100%) to the lower oxygen levels exhibited during the process run (30-60%) intensifies the possibility for measurement error. Over time, as the luminophore ages, the non-linear relationship curve between oxygen and sensor output will change. This shift in the curve can add further error into the difference between the offset value obtained with a product calibration and the actual measurement output.

After SIP, the optical DO sensor may experience a time period of elevated pressure during cooling and purging of the vessel. The net effect of this overpressure period is an artificially suppressed oxygen reading. The sensor can take several days to completely recover from overpressure, so a product calibration is typically performed when a seemingly stable reading is reached instead of waiting for full recovery. Depending on the amount of pressure and elapsed time after overpressure, the oxygen reading can be 3 to 9% lower than normal at the time of product calibration.

How Verification Relates to Product Calibration

As noted above, neglecting humidity and atmospheric pressure during calibration can lead to a maximum error of 10%. While product calibration corrects for some of this, many users perform a post-run verification. The verification compares the measurement value in air against the initial calibration of the sensor. This as-found/as-left methodology captures the effects of the process on the DO measurement.

Verification follows the same procedure as initial calibration but calculates error instead of adjusting the sensor output. Variances in verification calculations can lead to frequent calibration, sometimes after every run. Verification errors above 10% (typical for many customer operations procedures) require a time consuming deviation report, thus should be avoided at all cost. It is not uncommon with current optical DO technology to exceed the 10% error level after only 2–3 runs even with a perfect calibration.

Sources of oDO Sensor Drift During Process

Optical DO sensors rely on a silicone-based, luminescent coating for their measurement. The coating is bonded to a glass window, thus traditional limitations of gas permeable membranes found on polarographic sensors are not a concern. Unfortunately optical measurements are not foolproof, and there are process-related and internal factors that can cause undesirable deviation during the run.

Process Effects

There are certain chemicals that should be avoided when using typical oDO sensors, including:

- **Strong oxidizing chemicals** — Avoid long term exposure to strong oxidizers such as chlorine-based sanitizers. They can chemically bleach the luminescent coating causing a potential total loss of measuring capability (see Figure 10).
- **Organic solvents and long-chain hydrocarbons** — Liquids that can chemically attack silicone should also be avoided. Organic solvents may exhibit a leaching effect for the luminescent compounds used in the silicone coating. Long-chain hydrocarbons (C6+) can chemically attack the silicone thus stripping it from the optical window.
- **Oleic Acid** — Oleic acid, a major component of olive, canola, and other oils is somewhat common in biopharma fermentation processes where frequently SIPs are performed and can cause measurement problems for oDO sensors.

An oDO Cap with a protective PTFE layer can be employed to overcome oleic acid issues. The PTFE layer allows oxygen to permeate while blocking the chemical attack of oxidizing chemicals, organic solvents, and oleic acid, resulting in extended lifetime of the cap in these measurement conditions (see Figure 10).

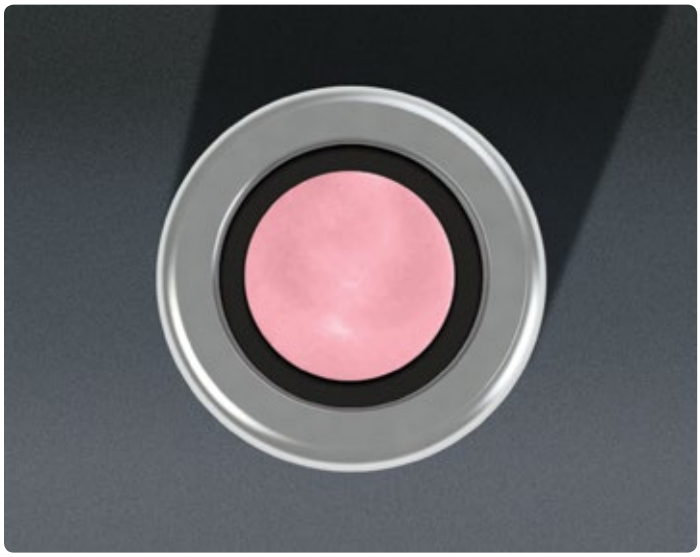


Figure 9. New Cap shows a pink-ish color when exposed to ambient light.

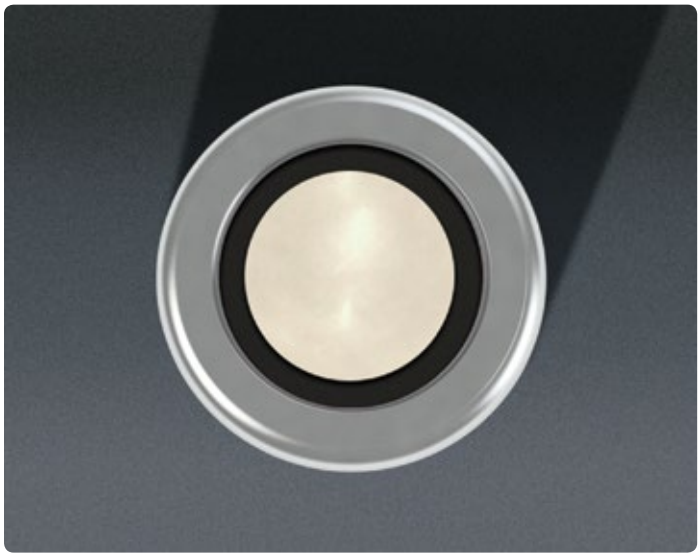


Figure 10. Used Cap exposed to strong oxidizers is bleached white and emits no color.

Cleaning and Sterilization Effect

The exposure to high temperature during Sterilize (or Steam) In Place (SIP) can accelerate the degradation of the luminescent sensing element used in optical DO sensors. The elevated temperature of 121ºC or greater will alter the wavelength of the emitted light used for the optical measurement. The immediate effect is a shift above the expected oxygen value. Often this shift will be occurring during product calibration or even during the fermentation run, creating undesirable error. Repeated SIP cycles have a cumulative effect of upward drift on the sensor that can lead to additional calibrations and the need for more frequent sensor cap replacement.

Clean In Place (CIP) can also have an adverse effect on the DO measurement. The CIP process is performed at elevated temperatures from 60 to 115ºC. Hamilton has found that the combination of high temperature and sodium hydroxide (NaOH) has the opposite effect of SIP in that it causes a slight downward shift in the oxygen measurement.

Process Effects (Cont.)

Process Pressure

Throughout the sterilization and cell culture process, positive pressure must be maintained within the bioreactor to prevent potential contamination from outside air. Fluctuations in the reactor pressure directly impact the partial pressure of oxygen in the media and thus elevate the reading from the sensor. The process pressure is not accounted for during initial air calibration and may be at a different value than pressure occurring during the product calibration.

Large scale bioreactors will monitor the process pressure to check for clogging of off-gas vent filters. This same process pressure can be used to compensate the DO measurement from the sensor. If the pressure value is fluctuating, then this compensation may best be done within the process control system. If the pressure value is constant and well controlled then it may be substituted for the atmospheric pressure setting within the optical DO sensor programming.

Photobleaching

Photobleaching is an on-going ageing process inherent to the design of optical oxygen sensors. Each time an oxygen measurement is performed, a quick flash of light is emitted on the oxygen sensitive coating. The light causes the luminescent coating to change from a ground to excited state and light is luminesced back. Over time the continued cycling of light eventually leads to molecular damage of the luminophore. This damage results in a very slow reduction of luminescence emission intensity over time. While measurement accuracy is maintained over a broad range of luminophore health, there is a point where the emitted light is not strong enough to be read by the detector within the sensor. This loss of intensity is captured in Hamilton sensors by the quality indicator and can be seen in ArcAir Software.

Cumulative/Net Error

The effects of temperature, pressure, and humidity during calibration combined with the effects of SIP/CIP and photobleaching are somewhat in opposition to each other. However, it would be a dangerous mistake to assume the effects would cancel each other out. The net error accumulation of these factors is significant and can lead to frequent post-run verification deviations in GMP/FDA environments (see Figure 11).

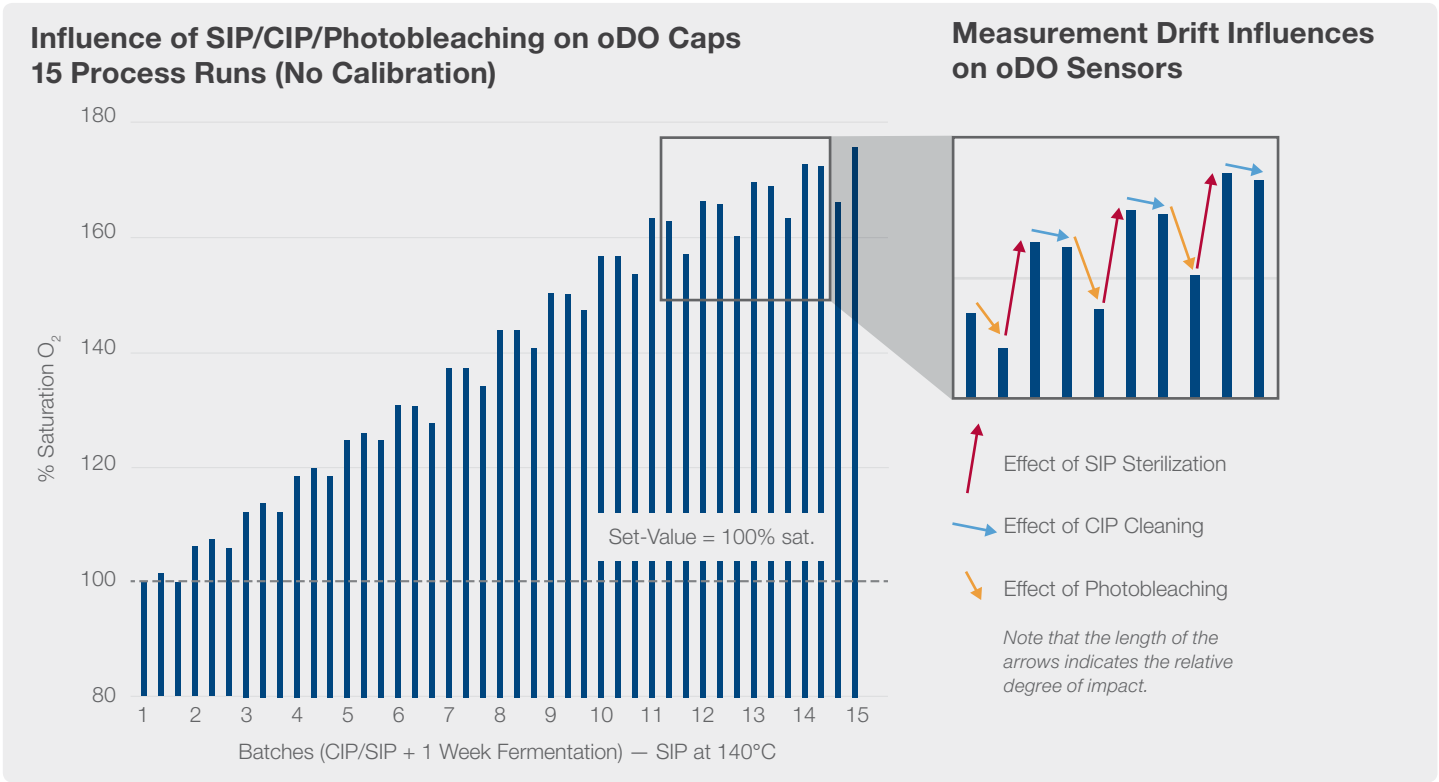


Figure 11. The cumulative effects of photobleaching, SIP, and CIP result in a net increase in DO reading at the time of verification. The set-value indicates the actual value of oxygen present.

Sensor Improvements: Minimizing Measurement Error

Based on insights gleaned from customer interactions, Hamilton has identified the primary sources of oxygen measurement error and channeled product development efforts into improved hardware and software for reducing the impact of these error sources.

Overcoming Calibration Hurdles with ArcAir Cal Wizard

To avoid errors due to humidity and atmospheric pressure, ArcAir Software Version 3.2 has built-in wizards. During calibration, verification, or product calibration, the customer is guided step by step through the process. The current atmospheric pressure and humidity can be accounted for by the customer within the wizard. Once calibration is complete, the software will revert automatically to the process humidity and pressure values stored within the sensor in order to be ready for the process installation.

There are many laboratory-style humidity and pressure measurement devices, the readings of which can be entered into ArcAir for a compensated calibration. If the atmospheric pressure in the lab is not measured and controlled, current conditions can often be found on the Internet (although they will not account for indoor conditions).

Sensor and Cap Improvement

Hamilton fully redesigned the sensor electronics and optical cap to create the most robust VisiFerm dissolved oxygen sensor yet. Upgrading both key components allowed the VisiFerm mA to have less frequent need for calibration, less measurement drift, and longer lifetime than previous oDO sensors.

Figure 12. Example of the calibration wizard within ArcAir Software Version 3.2.

Sensor and Cap Improvement (Cont.)

Cap Stability

The new Visiferm H3 and H4 caps have improved formulation and construction. These changes include:

- Strengthened luminophore matrix for better temperature stability
- Higher resistance to photobleaching
- Stronger mechanical and chemical stability for higher process resilience

The enhanced robustness can greatly increase the number of process cycles before requiring calibration or reaching a deviation level of error. This greatly reduced error can also be used to tighten the allowable tolerance before calibration if desired (see Figure 13).

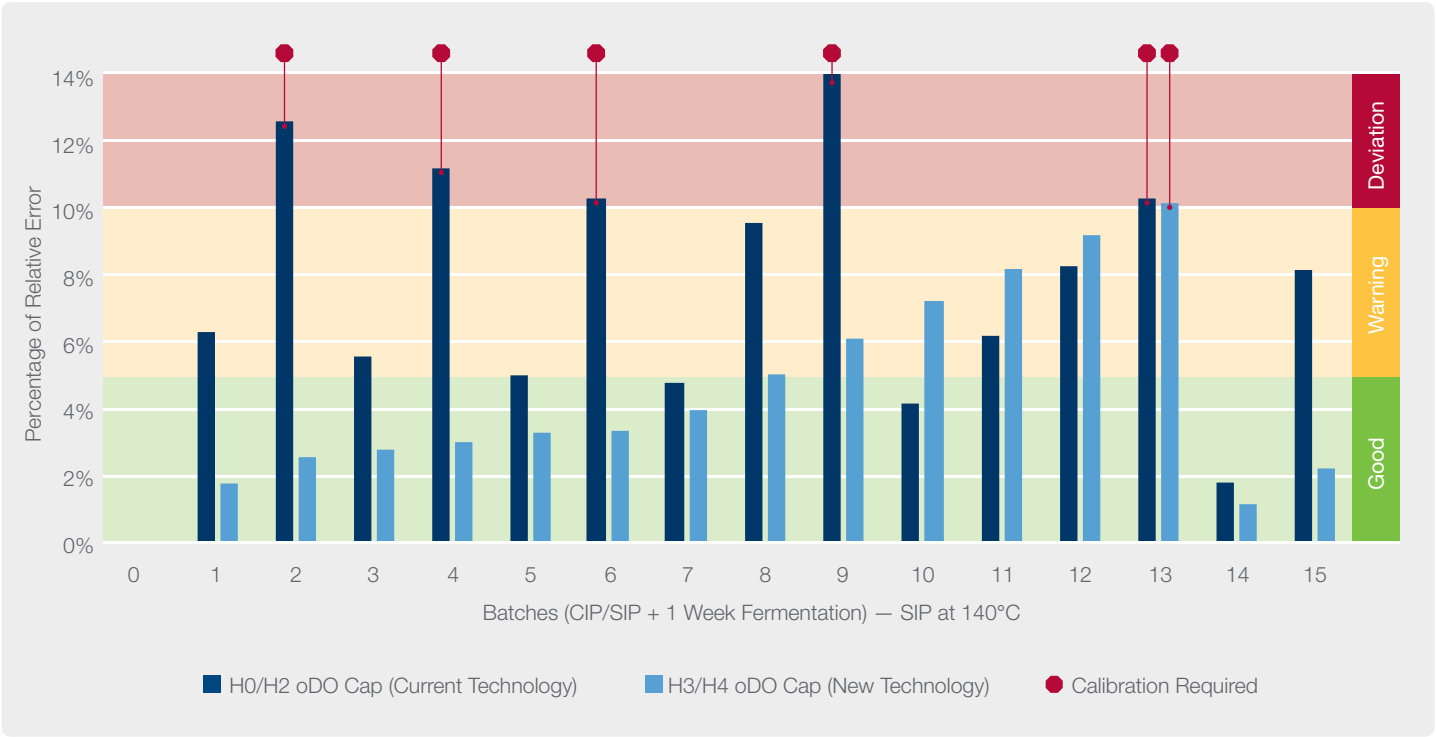


Figure 13. The previous generation of oDO caps (dark blue) could breach deviation tolerance after only 2 cycles (i.e. runs, processes, or batches), requiring frequent calibration. The newest oDO caps (light blue), designed for the VisiFerm mA can withstand 13 cycles before requiring calibration.

For applications with active chlorine, chlorine dioxide and lipophilic components the H4 cap combines all the benefits of the H3 cap with a newly designed PTFE coating to provide increased chemical resistance.

Sensor and Cap Improvement (Cont.)

Sensor Robustness

The VisiFerm sensor electronics have been revamped to better meet the requirements of the biopharma market.

- Tougher electronic components for higher temperature stability
- LED intensity adjustment reduce the impact of aging
- Increased memory for storage of enhanced diagnostic data
- Integrated Bluetooth 5 encrypted wireless communication
- M12 connector resistant to temperature and mechanical stress

Improved Diagnostics

The new ability to track changes in the cap and the electronics provides the opportunity for improved diagnostics for each component. The VisiFerm expresses each value as a percentage. A warning message will be displayed when these percentages reach levels that may affect the measurement. This can be used for real-time diagnostics or as a tool towards developing preventative maintenance schedules for changing the cap, performing calibration, or replacing the sensor (see Figure 14).

Sensor Health

Measurement Quality	Excellent
Sensor Quality	100%
Cap Quality	100%
Operating Hours	506.59 h
Max. Measurement Temperature	85°C
Operating Hours Above Max. Measurement Temperature	0 h
Max. Temperature	140°C
Operating Hours About Max. Temperature	0 h
Numper of SIP Cycles	0
Number of CIP Cycles	0

Figure 14. Example of the VisiFerm mA sensor health information displayed in ArcAir Software.

Conclusions

Optical DO measurement has been a great improvement over traditional polarographic technology commonly used in biopharma applications. Further improvements in DO measurement accuracy can be attained with better calibration tools, techniques, and innovative sensor design.

Current oDO sensors often reach dangerous levels of inaccuracy after the first post-calibration run, requiring frequent recalibration. This growing inaccuracy, or measurement error, is the result of exposure to elevated temperature (SIP/CIP), process chemistry, pressure, and on-going photobleaching. The next-generation VisiFerm mitigates the compounding of this error for reduced risk of process deviation, less calibration time and labor, and better accuracy for improved oxygen control.

Employing the VisiFerm mA can yield:

- 80% Fewer Calibrations
- 3x Longer Cap Life
- 50% Longer Sensor Life

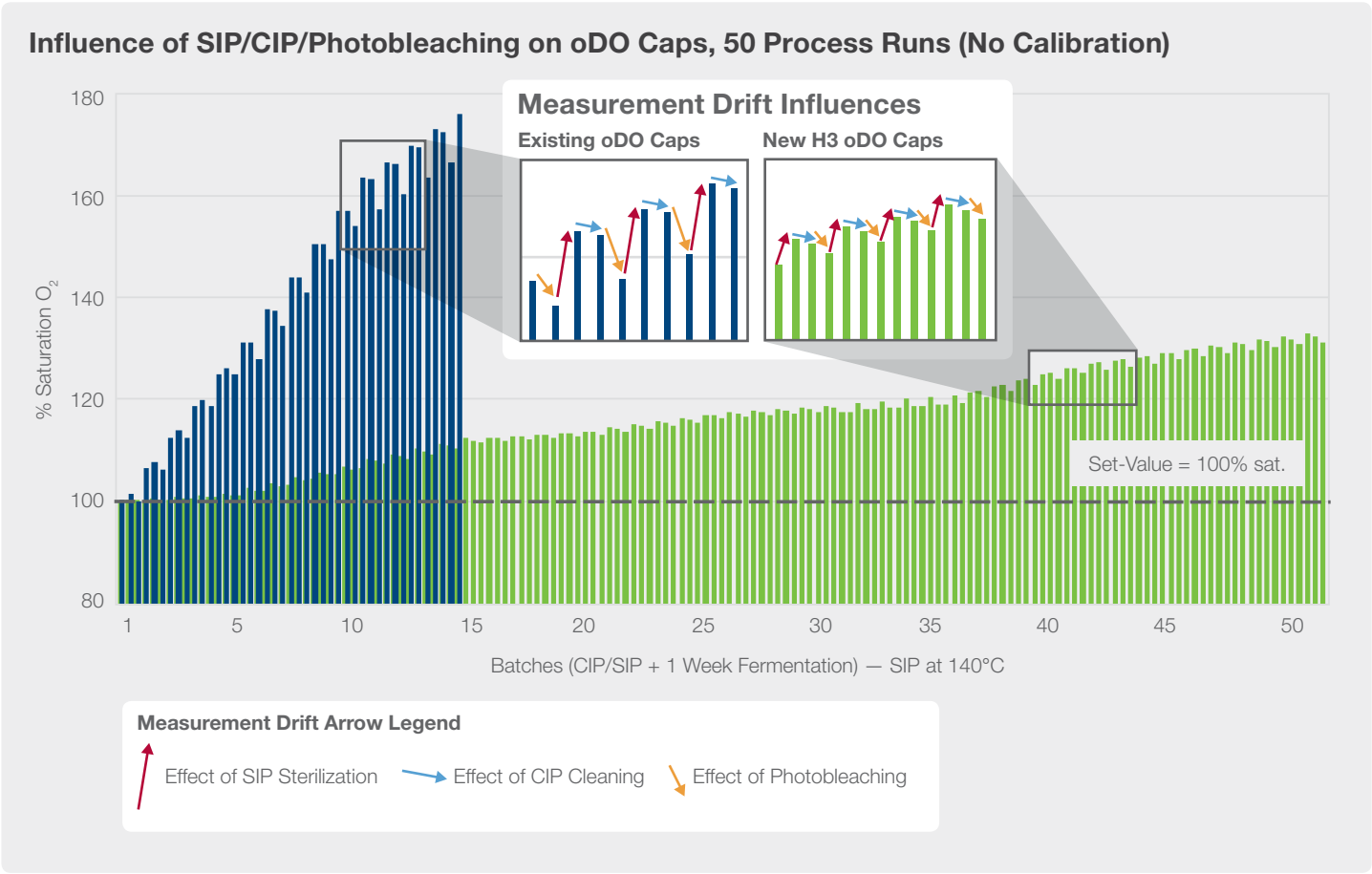


Figure 15. When measuring in 100% sat. O_2, previous versions of oDO sensors read over 110% after only 3 process runs. With the newest, most robust oDO sensor on the market, the VisiFerm mA, 15 process runs can be performed without recalibration before 110% is measured. After 50 runs, the VisiFerm mA only reads around 30% too high, a level reached after only 7 runs of the previous best-in-market sensor.

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HAMILTON®

Web: www.hamiltoncompany.com
USA: 800-648-5950
Europe: +41-58-610-10-10

Hamilton Americas & Pacific Rim
Hamilton Company Inc.
4970 Energy Way
Reno, Nevada 89502 USA
Tel: +1-775-858-3000
Fax: +1-775-856-7259
sales@hamiltoncompany.com

Hamilton Europe, Asia & Africa
Hamilton Bonaduz A.G.
Via Crusch 8
CH-7402 Bonaduz, Switzerland
Tel: +41-58-610-10-10
Fax: +41-58-610-00-10
contact.pa.ch@hamilton.ch

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