

Pharmaceutical

Perspectives in Liquid Process Analytics



21 News

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Exceptionally Stable Optical DO Sensors Novozymes Sees the Light

During the production of enzymes, ideal growth conditions must be maintained in bioreactors to maximize yield and ensure final product quality. Tight control of dissolved oxygen (DO) levels is central to this and to energy efficiency. Therefore, monitoring DO over long batch runs requires sensors with minimal drift. For Novozymes, optical technology provides the solution.

World leader in enzyme production

Novozymes, headquartered in Kalundborg, Denmark is the world leader in the production of enzymes and has a global market share of more than 30%. It produces a wide array of products for accelerating production processes for industries as diverse as agriculture, biopharma, food and beverage, and household care.

All of Novozymes' enzymes are produced via a similar fermentation process using either bacteria or fungi. To maximize enzyme yield and efficacy, ideal growth conditions in the fermentation broth must be maintained throughout the batch run. This necessitates tight control of a number of process analytical parameters including dissolved oxygen. DO measurement

and control is crucial for keeping cell growth on a set track, for the regulation and dosage of materials fed to the bioreactor vessel, and for optimizing air compressor use.

Investigation of amperometric DO sensors

For many years, Novozymes has used amperometric sensors for DO monitoring. But plant technician, Martin Falk, is well aware of the measurement drift that occurs with amperometric probes, and early in 2012 he conducted an evaluation of the performance of the sensors used at their facility. The accuracy of the signal, as well as the maintenance, handling, and robustness of the sensors were all thoroughly investigated. Although measurements were in line with expected values, Mr. Falk

**METTLER TOLEDO**



noticed that the stability and the handling procedures had room for improvement. He began to look at alternative solutions and became particularly interested in optical sensors.

Stable in measurement, low in maintenance

DO sensors based on optical measurement have two significant advantages over amperometric designs: Firstly, due to the nature of the technique, optical sensors are very stable even over long fermentation runs and therefore provide a more precise measurement; and secondly, they are low on maintenance. For these reasons, Mr. Falk decided to test METTLER TOLEDO's optical DO sensor InPro 6860 i.

As well as providing very accurate DO determinations, the InPro 6860 i has a hygienically polished surface finish for ease of cleaning between batches, making it highly suitable for fermentation applications. In respect of maintenance, instead of the replaceable membrane body, inner body, and electrolyte fluid found in amperometric sensors, only one component of the InPro 6860 i, the OptoCap oxygen-sensing element, requires periodic exchange. The sensor also features Automatic Stability Control for high, long-term, signal reliability.

Built-in intelligence

As well as the excellent measurement accuracy, low drift, and minimal maintenance Martin Falk was also impressed with the sensor's Intelligent Sensor Management (ISM[®]) technology. ISM is METTLER TOLEDO's innovative concept for process analytical measurement solutions that simplifies sensor handling, enhances process integrity, and reduces sensor lifecycle costs. Like all ISM sensors, the InPro 6860 i has an in-built microprocessor. This allows a number of valuable features, outlined below, that analog sensors cannot provide.

Secure calibration away from the process

ISM sensors retain their own calibration data on the installed microprocessor. The InPro 6860 i can therefore be calibrated away from the clean room environment in a more convenient location such as a lab. Using iSense software running on a PC or laptop and a USB connection, the sensor can be accurately calibrated and then stored until it is needed. According to Mr Falk, bringing an already calibrated sensor to the fermentation vessel saves 20 minutes for each batch.

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InPro 6860 i optical dissolved oxygen sensor



Plug and Measure feature

When a pre-calibrated sensor is connected to an ISM transmitter, the calibration and other configuration data held on the sensor are automatically uploaded and the transmitter configures itself appropriately. This significantly reduces the time required before the system can start measuring, and removes the risk of an operator entering incorrect data to the transmitter.

Predictive diagnostics

The InPro 6860 i monitors itself for wear and translates this information into predictive diagnostics tools. These provide a real-time display of sensor "health" and mean that any necessary maintenance

can be conducted before the batch, ensuring the sensor will operate reliably throughout the run.

Optical is the way forward

Thorough testing by Novozymes confirmed the InPro 6860 i's measurement stability, and showed that handling of the sensor was less cumbersome and time consuming compared with the amperometric probes they were using. Analysis revealed that the return on investment for the optical measurement system would be reached in two years.

Novozymes has installed the InPro 6860 i on all its production and pilot plant reac-

tors at its Kalundborg facility, and have kept the amperometric sensors as redundant measurements. On each reactor they have also installed the M800 multi-channel, multi-parameter transmitter which accepts the InPro 6860 i and other ISM sensors.

Martin Falk is very satisfied with the performance of METTLER TOLEDO's solution, "The new system is more stable and is more robust. The ideal would be to replace all amperometric sensors with optical ones in the future."

Find out more about optical DO sensors at:
► www.mt.com/InPro6860i

30 % Reduction in Plasma Fractionation Time Thanks to In-line Turbidity Measurement

Efficient cold ethanol fractionation requires tight turbidity monitoring. For one of India's main producers of plasma-derived therapies, switching from off-line to in-line turbidity measurements has significantly improved process productivity.

Producer of plasma-derived proteins

Intas Biopharmaceuticals Ltd. of Ahmedabad, India is one of Asia's leading producers of follow-on biologics. The company has fully-integrated biopharmaceutical operations with an R&D facility and an EU-GMP certified manufacturing plant. Celestial Biologicals, a subsidiary of Intas, focuses on the production of plasma-derived therapies; mainly albumin, immunoglobulin, and coagulation factors.

Fractionation process

In the cold ethanol fractionation process Celestial Biologicals use, ethanol at around -4°C is added to a quantity of human plasma. Ethanol concentration is increased in stages from 0 % to 40 %, while the pH of the fluid is lowered from neutral to about 4.8. At certain combinations of ethanol concentration and pH level, proteins precipitate out of the solution and are removed by centrifugation.



The turbidity of the solution increases with an escalation in precipitation until turbidity remains stable, indicating maximum fraction precipitation has been reached. For efficient yield, this point, called "holding time", must be clearly identified. Company technicians had been determining the holding time in the lab from grab samples. This was a time-consuming step and caused the fractionation process to be much longer than was desired. METTLER TOLEDO was asked to supply a system that would provide continuous, real-time data

and therefore eliminate the need for grab samples.

In-line turbidity measurement

We installed a system comprising the InPro 8200 turbidity sensor, InFit 761 housing, and Trb 8300 transmitter. The real-time data from the in-line sensor allows the facility's technicians to track how turbidity changes as ethanol concentration and pH level are altered, and to quickly identify when a holding time is reached.

Process time reduced by 30 %

Celestial Biologics are very pleased with the system's performance. The continuous turbidity measurements have made a dramatic improvement to the process and reduced fractionation time by around a third. In addition, they are also successfully using the system to check filter performance before and after centrifugation.

Find out more about in-line turbidity monitoring, at:

► www.mt.com/turb

In-line turbidity measurement improves processes, and saves time and costs

Measuring turbidity in-line using a METTLER TOLEDO measurement system has many benefits:

- Real-time detection of abnormal conditions
- Real-time determination of batch end
- Saves off-line measurement laboratory costs and time

Discover more at:

► www.mt.com/turb

InPro 8200 Turbidity Sensor



Improved process control

- Reliable and reproducible detection of turbidity thanks to dual-fiber optical technology

Reduced investment

- Suitable from laboratory benchtop level through to commercial process installations due to compact 12 mm design

Enhanced process safety

- Easily cleaned and fouling-free owing to uniform, unbroken sensor surface

Trb 8300 Transmitter



Precise calibration

- Advanced calibration routines ensure reliable and repeatable measurements

Minimal configuration

- Switch easily between customized parameter sets for different applications

Reduced start-up time

- Three selectable dialog languages and online help for user-friendly set up

Remote Access to Sensor Diagnostics

New FF Transmitter

The M400FF transmitter with Intelligent Sensor Management (ISM®) technology provides the highest reliability and easiest handling in hazardous and non-hazardous area applications. Advanced sensor diagnostics data available over FOUNDATION fieldbus™ leads to reduced operating costs and helps improve productivity.

Outstanding reliability

With its rugged design and approvals for hazardous area use, the M400FF 2-wire transmitter provides operating assurance even in the most challenging conditions. In combination with METTLER TOLEDO's advanced Intelligent Sensor Management (ISM) technology, the M400FF offers greater process reliability in pharmaceutical applications.

Flexible and future-oriented

The M400FF transmitter is a multi-parameter, single-channel unit for pH/ORP, amperometric and optical oxygen, conductivity, and dissolved carbon dioxide sensors. Thanks to the mixed-mode input, which accepts traditional analog or ISM sensors, the M400FF offers a unique and

smooth technology transition from analog to digital sensors and provides a future-oriented investment in your plant.

Compatible with your asset management system

Because of the implemented standardized FOUNDATION fieldbus (FF) interface, the M400FF supports corresponding asset management tools, such as AMS (Emerson) and PRM (Yokogawa), and field communication tools including HH475. This ensures maximum compatibility with your asset management system.

Quick set-up and simplified sensor handling

Thanks to the M400FF's advanced ISM functionality, the transmitter offers ad-

ditional, valuable benefits:

- Using our iSense software for ISM sensors, probes can be accurately calibrated in any convenient location and stored for later use.
- When a calibrated sensor is connected to the M400FF, the calibration data is automatically uploaded and the system is ready to measure in a few moments.
- This Plug and Measure feature minimizes the risk of installation troubles and simplifies sensor commissioning and replacement.

Improved process control thanks to sensor diagnostics

Measurement data and ISM sensor diagnostics tools such as the Dynamic Lifetime Indicator (DLI), Adaptive Calibration Timer (ACT) and Time to Maintenance (TTM) can be integrated into the process control system. Due to the M400FF's communication capability, system integration is easily achieved, enabling more efficient maintenance of the measurement system. Unplanned shutdowns due to unforeseen sensor failure no longer occur, and the resulting increase in process availability and reduced maintenance lead to improved productivity and lower operating costs.

Find out more at:

► www.mt.com/M400-2wire



Meet Regulatory Requirements with Low Maintenance Measurement Systems

METTLER TOLEDO offers a wide portfolio of sensors, transmitters, housings, and sensor cleaning systems to provide solutions tailored to your precise needs. For a US biopharma company, we supplied exactly the pH measurement solution they required.

Wastewater must meet EPA standards

The global biologics business unit of a major pharmaceutical company operates a number of production facilities in Europe and the United States.

To meet Environmental Protection Agency (EPA) requirements at their US production plant, wastewater is treated then neutralized in holding tanks before being discharged to the municipal sewer system. In compliance with EPA regulations, pH is adjusted to between 6 and 9 prior to release.

Low maintenance pH system required

For pH measurement, plant technicians were using sensors installed in static housings. Process conditions caused sensor coating which required weekly cleaning, a procedure that involved draining the holding tanks to allow access to the probes. The inconvenience and time involved in maintaining the pH sensors encouraged the company to ask METTLER TOLEDO for systems that would not involve tank draining and would reduce the time spent on sensor maintenance, while ensuring the water was in compliance with EPA regulations before discharge.

METTLER TOLEDO solution ticks all the boxes

We supplied systems comprising an InPro 4260 i pH sensor, InTrac 777 retract-

able housing, M700 transmitter, and EasyClean 400 automated cleaning/calibration system: a solution that meets all requirements.

Low maintenance pH sensor: InPro 4260 i

- Polymer reference electrolyte for extended sensor life
- Open junction eliminates clogging
- Sensor diagnostics for predictive maintenance

Retractable housing: InTrac 777

- Sensor can be removed without process interruption
- Tri-Lock™ safety system prevents escape of medium when sensor is removed

Modular and adaptive transmitter: M700

- Multi-parameter unit configurable via slot-in modules
- Advanced sensor diagnostics

Automatic sensor cleaning and calibration with EasyClean 400



Automatic sensor cleaning/calibration: EasyClean 400

- Minimum maintenance costs by fully automatic pH sensor cleaning and calibration
- High flexibility due to freely programmable sequences

The systems are providing dependable, real-time measurements, and are allowing technicians to concentrate on more critical tasks.

If you need a measurement solution tailored to your requirements, go to:

► www.mt.com/PRO

Monitoring Cell Culture Bio-Processes In Situ and in Real-Time

ReactIR™ and Focused Beam Reflectance Measurement (FBRM®) are proven in situ technologies for real-time monitoring of principle bioprocess components and changes in cell density. This article highlights the results of two applications, both demonstrating the value of in situ ReactIR™ and FBRM® in bioprocess monitoring.

With the increase of biopharmaceutical drugs on the market in recent years, research focus has turned to optimizing bioprocesses in order to maximize product recovery and improve product quality through the use of Process Analytical Technologies (PAT). Off-line techniques for monitoring cell cultures are time consuming, may require sample preparation, and do not provide real-time bioprocess information, which restricts the ability to control the process. Non-invasive and non-destructive in situ probe-based technologies monitor processes in real time by providing information about the bioprocess as it exists in the bioreactor.

Monitoring carbon source and metabolites

ReactIR™ is an ATR mid-IR spectrometer equipped with a DiComp probe. The ability of ReactIR™ to monitor the concentrations of four principle analytes: glucose, L-glutamine, lactose, and ammonia in a mammalian cell culture was determined by comparison to off-line enzymatic as-

says (Megazyme, Ireland). The data in figure 1 demonstrates how ReactIR™ was able to monitor component concentrations at both high and low concentrations.

As cells metabolize glucose and glutamine, lactate and ammonia are produced, respectively, meaning there is a strong correlation between the metabolically related components. To confirm that ReactIR™ monitors each component independently of the other, further experiments tested the calibration models. In the example shown in figure 2, glucose was spiked into a solution of lactate, and ReactIR™ spectra were collected. The data confirms that changes in glucose concentration did not affect the measurement of lactate even when the sample was spiked with 30 mM of glucose.

Monitoring cell density

The in situ monitoring of cell density changes was proven using FBRM® which counts cells and measures cell dimensions. Cell counts determined by FBRM®

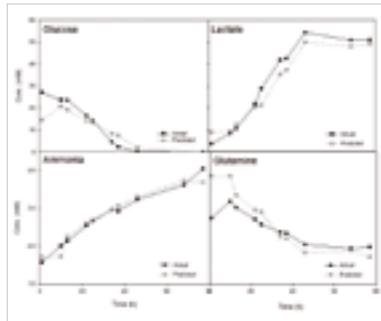


Figure 1. Actual and predicted values for four principle components of a cell culture.

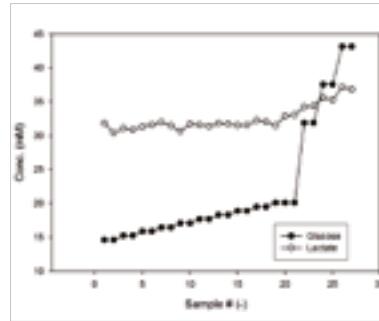


Figure 2. Changing glucose concentration does not affect the lactate concentration as measured by ReactIR™.

demonstrated a strong linear relationship with cell density with a coefficient of determination greater than 0.99 (figure 3).

Conclusions

The non-invasive and non-destructive in situ, real-time monitoring of principle components and changes in cell density, as they exist in the reactor, is possible with ReactIR™ and FBRM®, respectively. ReactIR™ and FBRM® eliminate the need for sampling and sample workup, while reducing the risk of contamination. The real-time information provided by ReactIR™ and FBRM® enables bioprocess understanding and immediate process control.

Text: B. Rice, University College Dublin.

► www.mt.com/ac-biotech

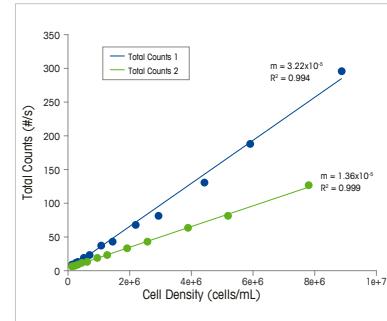


Figure 3. Effect of cell density on total cell count as measured by FBRM®.

Purified Water



Accurate, Reliable, and Easy to Use

Three Reasons Why ELGA Trusts Thornton

When accurate water measurements are vital, high-performance analytical sensors must be used with an equally high-performance transmitter. For ELGA Process Water, the reliability, durability and simple operation of METTLER TOLEDO Thornton instruments gives them "peace of mind".

Eight decades of water treatment experience

ELGA Process Water, part of Veolia Water Solutions & Technologies, specializes in delivering innovative solutions for all pharmaceutical process water and wastewater needs. ELGA Process Water has over 75 years' experience in water treatment and has completed more than 30,000 installations. The company selected METTLER TOLEDO Thornton M300 transmitters to incorporate in their modular pure water systems because of their accuracy, reliability, and ease of use.

The ORION® Modular Pure Water Solution

ELGA's ORION® packaged systems are prevalidated, skid-mounted, and hot water sanitizable. With 80 different options, the ORION® can meet the water quality standards of ISPE, USP, Ph Eur Purified Water, and Ph Eur Highly Purified Water, and is fully compliant with FDA, cGMP, and GAMP requirements.

Designed with high-quality components, ORION® systems include Thornton pro-

cess analytical instruments with advanced sensor technology. The M300 transmitter, a standard in the ORION® system, with its proven excellence in performance and accuracy, provides reliable measurement of conductivity, which is critical for pharmaceutical purified water.

The system incorporates two M300 transmitters and three Thornton sensors to measure water conductivity before and after the reverse osmosis unit, and after the continuous deionisation polishing unit. These measurements ensure that the system is working to optimum performance, while the final sensor verifies the conductivity in accordance with USP/Ph Eur Pharmacopeia specifications for purified water.

In addition to monitoring during normal operation, these sensors must also be able to withstand the ORION®'s periodic hot water sanitization (HWS), where the system is sanitized to above 80 °C for one hour per cycle. The Thornton sensors continue to supply accurate readings in excess of 250 HWS cycles, while proving the efficiency and reliability of both the sensors and the ORION® purified water system.



ORION® modular pure water solution

Ranj Rihal, Pharmaceutical Market Coordinator at Veolia Water Solutions & Technologies explained, "Incorporating Thornton instruments gives ELGA Process Water the peace of mind that high pharmaceutical industry standards are achieved with proven validated results."

M300 instrumentation

METTLER TOLEDO Thornton provides ELGA Process Water with conductivity systems using the M300 dual-channel conductivity transmitters. This allows for two conductivity sensors to be connected into the same transmitter allowing comparison between two sensor values to cal-

culate membrane performance. The M300 comes in two convenient sizes, $\frac{1}{4}$ DIN specifically for panel mount applications, and $\frac{1}{2}$ DIN for field, post, or wall mount applications.

The Thornton M300 series of process analytical instruments provides this flexibility



with single-channel, multi-channel, and multi-parameter models that can measure conductivity/resistivity, pH/ORP, dissolved oxygen, ozone, and flow.

Find out more about the M300 at:

► www.mt.com/M300

Complete CIP Control with UniCond® Conductivity Sensors

The new, digital, four-electrode, UniCond conductivity sensors measure up to 1,000,000 $\mu\text{S}/\text{cm}$ for clean-in-place and other chemical concentration measurements.



Process compatibility

CIP and other process applications often require compact, in-line sensors for concentration control. UniCond conductivity sensors are offered with Tri-Clamp® and NPT process connections and FDA-compliant USP <88> Class VI PEEK polymer, with ratings to 140 °C for full process compatibility.

Accurate calibration

With conventional conductivity instrumentation, verification and calibration

involve the sensor, the cable, and the measuring instrument. Each of these can contribute error to the measurement and so they must be calibrated together as a system, in situ.

Now, with the new UniCond 4-E sensors, the measuring circuit, analog-to-digital conversion, and full sensor data including calibration memory are all contained within the sensor body. No error is introduced by the digital cable or instrument. For periodic calibration or verification, the

sensor can be removed and recalibrated remotely or it can be calibrated in place; either way, full accuracy is achieved.

For processes involving chemical concentration measurements, METTLER TOLEDO Thornton provides the most advanced and convenient solution.

Find out more at:

► www.mt.com/UniCond

Maintain Ideal Growth Conditions in Mammalian Cell Culturing

High levels of dissolved carbon dioxide during mammalian cell culturing can inhibit cell growth and metabolism. In-line measurement allows closed-system control for retaining a healthy environment for the cells. The InPro 5000i sensor combines precise and reliable measurement of dissolved CO₂, with the performance benefits of Intelligent Sensor Management (ISM®).

Maintaining the ideal dissolved CO₂ level in bioreactors produces a higher quality product and reduces run time. The InPro 5000i sensor provides very accurate CO₂ measurements and is simple to handle.

Its robust and fully sterilizable design meets all requirements for hygienic processes.

ISM technology provides sensor relevant information for maintenance planning, and pre-batch or real-time diagnostics.

For full traceability, all pertinent data such as calibration details and number of SIP cycles or autoclavings are stored inside the sensor.

Plug and Measure with factory-calibrated sensors sets a new benchmark in simplicity for in-line dissolved CO₂ measurement.

Find out more at:
► www.mt.com/InPro5000i

Your benefits



Pre-batch diagnostics

Determine if maintenance for the internal electrode is required before next fermentation run.



Lower operating costs

High process tolerance means less maintenance and fewer internal electrode replacements.



Simple calibration

Two-step calibration is not required. Only a process calibration is needed.

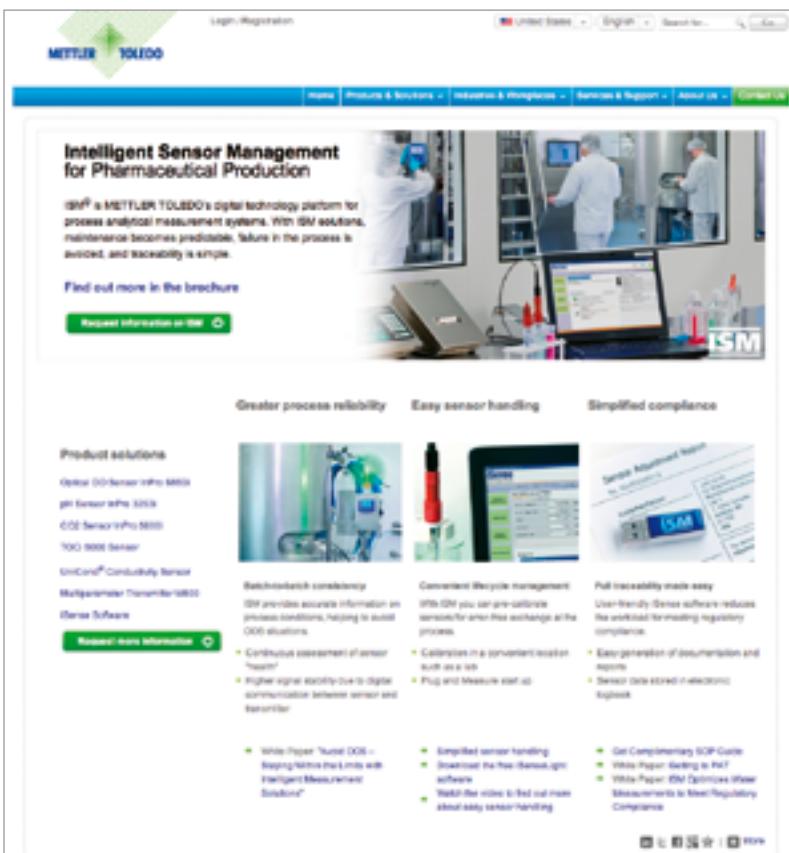


InPro 5000 i dissolved CO₂ sensor

SM



Get in-line with METTLER TOLEDO



The screenshot shows the METTLER TOLEDO website with a green header. The main content area features a large image of a pharmaceutical production line with workers in cleanroom suits. The text "Intelligent Sensor Management for Pharmaceutical Production" is displayed above the image. Below the image, there are three sections: "Greater process reliability", "Easy sensor handling", and "Simplified compliance". Each section has a small image and a brief description. The "Greater process reliability" section shows a sensor in a process line. The "Easy sensor handling" section shows a sensor probe and a tablet. The "Simplified compliance" section shows a document with "ISM" on it. On the left side, there is a sidebar with "Product solutions" and a "Request more information" button. The footer of the page includes social media icons and a "Print" button.

Intelligent Sensor Management for Pharmaceutical Production

ISM® is METTLER TOLEDO's digital technology platform for process analytical measurement systems. With ISM solutions, maintenance becomes predictable, failure in the process is avoided, and traceability is simple.

See the complimentary brochure, white papers, and software on our website for the pharmaceutical industry and discover how ISM delivers:

Greater process reliability

Easy sensor handling

Simplified compliance

► www.mt.com/ISM-pharma

