CELTIC ADVANCED LIFE SCIENCE
INNOVATION NETWORK

CALIN

RHWYDWAITH GELTAIDD
ARLOESI GWYDDORAU
BYWYD UWCH

Inline process monitoring technology: Vision for the 2020s

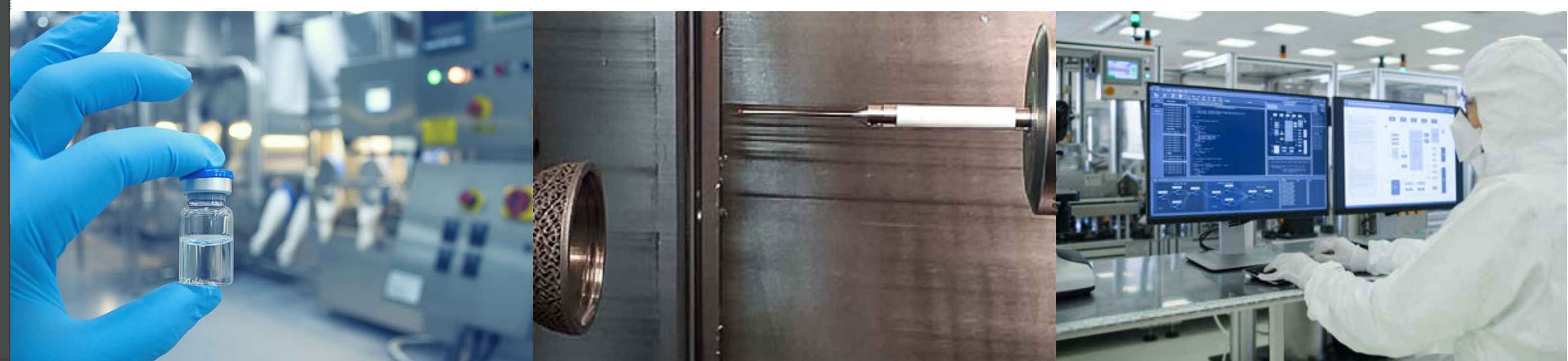
Dr Patrick Sugrue
CALIN Research & Development Innovation Officer
Tyndall National Institute

CELTIC ADVANCED LIFE SCIENCE
INNOVATION NETWORK

CALIN

RHWYDWAITH GELTAIDD
ARLOESI GWYDDORAU
BYWYD UWCH

Contents



Inline process monitoring technology research overview

Inline process monitoring uses sensors integrated into the production process to measure quality parameters in real time. Online monitoring removes samples of product from the main process and directs these samples to sensors to perform quality checks at specific times. The objective is to automate the monitoring process to facilitate intervention when a batch is at risk of failing to meet quality expectations and yield. At-line monitoring usually involves manually sampling the product, usually at the end of a process step to verify that an expected quality level had been achieved. Highly regulated industries such as the food and beverage (F&B), oil and gas, water treatment, pharmaceutical and biopharmaceutical industries have been developing process monitoring technology for decades. Tyndall's research interest lies in the development of process analytical technology (PAT) for the industries mentioned above with a special interest in the biopharma and emerging cell and gene therapy (CGT) industries. Parameters of interest include temperature, dissolved oxygen, pH, glucose, lactate and ammonia. The quality and yield of biopharmaceutical medicines generated by a mammalian cell culturing process is dependent on the control of these parameters. The US food and drug administration (FDA) are now encouraging pharma companies to adopt a quality by design (QbD) approach and build quality into the product development from the start. PAT plays a key role in delivering QbD. This is achieved by using sensing technologies throughout the production process. Sensors come in all shapes and sizes. Most are currently packaged into industry standard probes. These are inserted into the bioreactors or mixers. These sensors can be electro-chemical or optical. Optical probes have the advantage of being contactless and are easier to achieve bio-compatibly with reduced risk of product contamination. However they are expensive and have a slow response. Electro-chemical sensors are cheaper and respond faster than optical sensors. However, direct contact with the product is required and bio-compatibility and product contamination is a concern.

Why is Inline process monitoring technology important?

PAT is a broad topic with a variety of disciplines. Tyndall's interest is in the development of inline sensing and instrumentation systems that enable the biopharma and emerging CGT industry to optimise yield. Acceptable quality of biological medicines can be achieved with current PAT technologies but improvement in yield is desirable. Current inline industrial PAT implementations use probes that are fixed in one position. Each probe monitors a single parameter. Multiple probes are usually used in a typical PAT process. These configurations do not provide adequate monitoring of product homogeneity and aeration in large industrial vessels. PAT adoption has been mainly limited to laboratory R&D with the objective of process development prior to scale-up. Typical bioreactors have a limited number of probe ports. This limits the number of parameters that can be monitored at the same time. For example, typical parameters of interest for bio-pharma products are pH, dissolved oxygen and temperature. Suitable probes to measure these parameters are commercially available. Additional parameters such as glucose, lactate and ammonia would be desirable to include in the PAT process. Suitable probes to measure these extra parameters are not commercially available and commercial bioreactors do not always have enough probe ports to include them. Scaling up from the lab to pilot lines and commercial manufacture would improve quality monitoring, facilitate frequent sampling, batch-to-batch comparison and assist process transfer with the use of a process signature. A process signature established in a small scale laboratory based fixed probe bioreactor may not scale to a much larger industrial scale bioreactor. Tyndall has been addressing these challenges with the development of multi-parameter electrochemical sensor solutions. Different sensor modules can be incorporated into a single sensor system with a form factor that can fit existing commercially available bioreactors. Tyndall is currently working on extending this multi-parameter platform to include all the mentioned parameters along with a viable cell density measurement capability. For larger bioreactors, Tyndall has developed a wireless multi-parameter capsule that can be suspended in the media inside the bioreactor. These advancements push the inline PAT technology beyond the current industry state of the art.

Swansea University Prifysgol Abertawe · Cardiff University Prifysgol Caerdydd · Prifysgol Bangor University · UCD Dublin · NUI Galway OÉ Gaillimh · Tyndall National Institute Institiúid Náisiúnta

Application of Inline process monitoring technology in the current climate

Tyndall in collaboration with NIBRT (National Institute for Bioprocess Research and Training, Ireland) has developed a wireless PAT capsule (PATsule) platform capable of measuring multiple parameters (temperature, dissolved oxygen and pH). This technology provides a solution for continuous real-time monitoring of physical, chemical and biochemical parameters including metabolites in the media based on a novel autonomous multiparameter sensing systems which can be in the form of a miniature capsule suspended in the cell media, or for smaller bioreactors, as a multiparameter probe. The capsule is composed of a custom electrochemical sensor chip and instrumentation. The capsule electronics system is battery powered, performs the sensor interfacing functions, processes the sensor signals and communicates with an external control station. The external control station can be any process controller ranging from a simple laptop to an industrial SCADA system, located outside the bioreactor.

A scalable multi-parameter probe was developed during the H2020 AUTOSTEM project. The AUTOSTEM consortium developed an automated, sterile pipeline for large-scale production of therapeutic stem cells. The probe measured glucose, lactate and ammonia to support the culturing of stem cells in the bioreactor. The ultimate aim is to generate clinical quantities of high quality therapeutic stem cells at an affordable cost, thus enabling the routine clinical use of stem cell therapies in the future.

Potential impacts of Inline process monitoring technology in both academia and industry moving forward?

PAT advancements are required to achieve QbD and process scalability from laboratory scale through the different stages of process maturity (laboratory to full production). As more parameters are monitored, greater visibility into the process can be achieved. Currently, pH, temperature and dissolved oxygen are monitored during cell culturing. For example, the AUTOSTEM project consortium identified additional parameters as already mentioned. Existing commercially available bioreactors limit the number of probes to four typically. As existing commercially available probes measure one parameter, this limits the parameters that can be monitored.

Tyndall's approach was to develop a novel modular probe where more sensor modules can be added to a single probe. This can be an adequate solution for stem cell culturing applications where volumes are low. However, other cell lines, such as Chinese hamster ovary (CHO), can scale from 100L up to 20,000L. As volumes increase, fixed position probes become a disadvantage as already discussed. It is desirable to adopt a sensing methodology that can scale with the bioreactor volume as the process matures.

The PATsule approach is more sympathetic to scaling and allows visibility into homogeneity issues and allows a process at laboratory scale to be compared to the same process at pilot and production scales even though the bioreactor volumes being compared are different. There has been a growing trend in the development of modelling approaches in bioprocessing over the past 20 years with an increased interest in supervised and unsupervised machine learning algorithms.

Good Automated Manufacturing Practice (GAMP) requirements will challenge technology developers to provide safe solutions and future technology will have to be developed with these requirements in mind.

Swansea University Prifysgol Abertawe · Cardiff University Prifysgol Caerdydd · Prifysgol Bangor University · UCD Dublin · NUI Galway OÉ Gaillimh · Tyndall National Institute Institiúid Náisiúnta

Summary of thoughts and how is your institution working towards utilising this to drive innovation:

Tyndall is committed to driving technology advancements that optimise yield in biopharma and cell and gene therapy processes. Opportunities also exist in facilitating industry to scale these processes from laboratory scale to full production. These opportunities are being addressed with scalable sensor and instrumentation solutions that can be integrated into the automated control system for the process.

Technology developed during the PATsule and AUTOSTEM projects are exemplars of multiparameter sensors systems that advance the state of the art used by industry today (Patent applications in preparation). More parameters can now be monitored. More sensor parameters can enhance the visibility into the process and that can support the development of the quality by design approach encouraged by the FDA. The management of increased data volume generated by more parameter monitoring is a future challenge.

There is a growing interest in the use of machine learning algorithms to model bioprocesses and more parameters may achieve better modelling outcomes. Tyndall is working on integrating more sensors into the technology solution.

Tyndall's technology provides the multiparameter data which will be basis for decision support for optimisation of bioprocess yield, and will ultimately enable closed loop automated process control systems.

CELTIC ADVANCED LIFE SCIENCE INNOVATION NETWORK

CALIN

RHWYDWAITH GELTAIDD ARLOESI GWYDDORAU BYWYD UWCH

EU Funds: Ireland Wales Programme 2014-2020

Tionól Réigiúnach an Deiscirt Southern Regional Assembly

Cláir Chistí Eorpacha Struchtúrtha agus Infheistíochta na hÉireann 2014–2020

Cómhaoinithe ag Rialtas na hÉireann agus ag an Aontas Eorpach

Undeb Ewropeaidd European Union

Llywodraeth Cymru Welsh Government

Cronfa Datblygu Rhanbarthol Ewrop

European Regional Development Fund

Swansea University Prifysgol Abertawe · Cardiff University Prifysgol Caerdydd · Prifysgol Bangor University · UCD Dublin · NUI Galway OÉ Gaillimh · Tyndall National Institute Institiúid Náisiúnta