PHARMAprocess

Innovation Forum in Pharmaceutical Process

Maximizing efficiency: Process Analytical Technologies and Process Intensification

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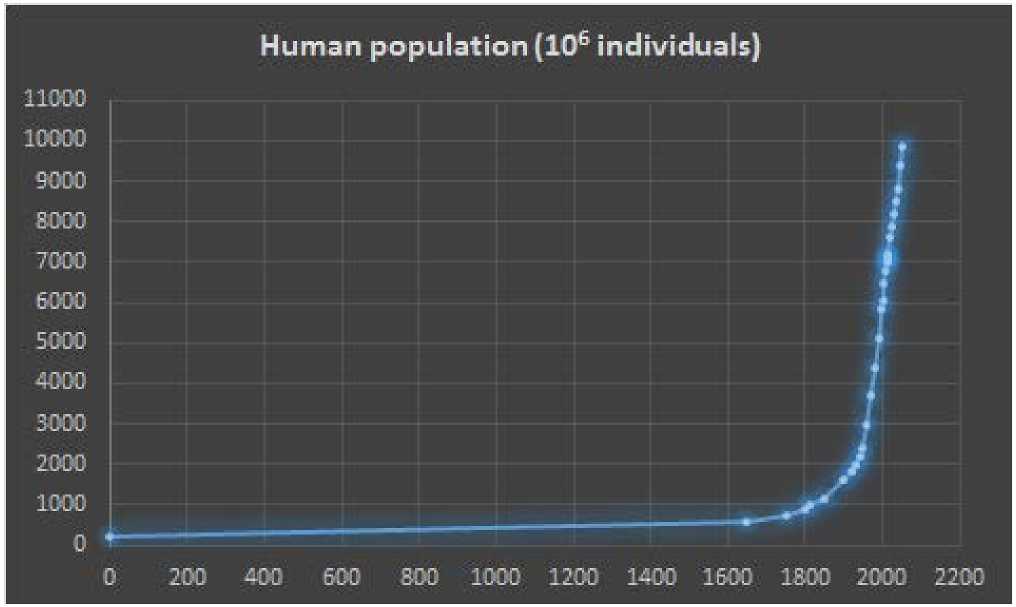
A challenge and a rational way to address its solutions

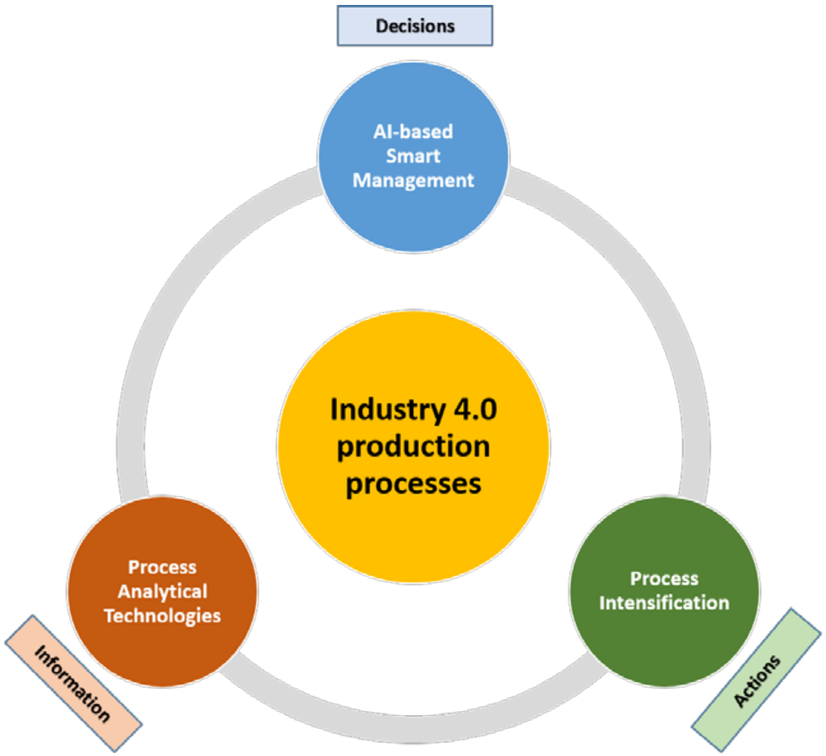
Sustainable development requires new paradigms



A challenge and a rational way to address the solutions

Sustainable development does require new paradigms

Our approach for contributing to achieve sustainable development in an expanding global economy is a crosslinked combination of **PAT**, **Artificial Intelligence-based management** and **Process Intensification**



Who we are and how we are contributing to PAT & PI

Innovació i Recerca Industrial i Sostenible, S.L. (IRIS)

An **advanced engineering** company specialising in **process monitoring and optimisation** with facilities in Barcelona and Dublin:

- IRIS Solutions: Advanced monitoring and control
- IRIS Research:
  - Spectroscopy technologies
  - Data processing and information systems
  - Novel processing technologies
  - Sustainable processing technologies

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Who we are and how we are contributing to PAT & PI

Multidisciplinary high qualified staff with business-oriented engineering and scientific skills and expertise: bridging the technological gap between the academia and the industry

IRIS has been successfully promoting, coordinating and providing technical solutions in **40** **FP7** projects and **12** **H2020** projects

AI-based management

Process Analytical Technologies

Process Intensification

PAT

Science-based knowledge about what is really taking place within the process

Process Analytical Technologies (PAT): Controlling the process by monitoring “target” features -what the process is aimed for- as opposed to merely supervising and adjusting the process conditions in line with the optimum parameters determined by the traditional recipe. Usually such target features are chemical or physical properties such as composition or particle size, that require analysers instead of mono-parametric probes.

Are PATs sufficiently implemented in pharma since the historic FDA statement?

> “Currently, the PAT segment of the market is 1/10 the size of the laboratory segment”
>
> [Richard Tweedie, Procedia Engineering 102 (2015) 1714-1725]

The Holy Grail in PAT could be a “plug & play smart analytical probe”, which is not available yet. In the mean time, **case-dependent integration** tasks have to be considered as the key factor for succeeding.

PAT

Implementation phases (PAT degrees)

1. Online or inline **analytical probes** placed in the CCPs. Requires ad hoc integration and chemometric models. In terms of process recipes, it can be considered simply as upgraded automation as the recipe does not change; it just provides just a deeper view of the process.
2. **Data mining** of the historian -previously existing datasets which are not necessarily collected by PAT analyzers- to generate **multivariate predictive models** for achieving better understanding about the process.
3. **QbD**: Designing or re-designing the process recipe from scratch on the basis of a DoE. Ideally, it should be tackled after installing PAT analyzers in order to run several cycles for gathering a comprehensive dataset of correlated process conditions and outputs. It enables an optimization of the **data-driven recipe** and could generate a model for controlling the process along the optimal path.

PAT

A proposal for fostering a PAT-oriented corporate culture

- Carry out an analysis in terms of opportunities: Higher envisaged **ROI** processes should have higher priorities
- Initially, do not link PAT to regulatory issues: PAT is primarily a tool for **keeping processes under control** around the optimal path; real-time release should be tackled once PAT is properly proven

  "The (often) months that it takes to complete a lot of drug are directly tied to old, "tried-and-true" analysis methods, where samples are sent to the lab and the materials sit on a shelf, waiting for an answer. The production machinery sits with plastic covers, waiting for lab reports on cleaning validation samples, and so on. Even if ... the quality remains the same as before PAT, the speed that the crap gets out the door is greatly enhanced...and hardware is utilized at a higher level, meaning fewer new pieces need be purchased ... Months become days..." E. Ciurczak comment to the PAT Group LinkedIn post "PAT Guidance 10 years on. How far have we come?" (June, 2014)

- Structure the PAT implementation stage-by-stage: Small goals implies easier troubleshooting; a robust way is built with small successful steps.

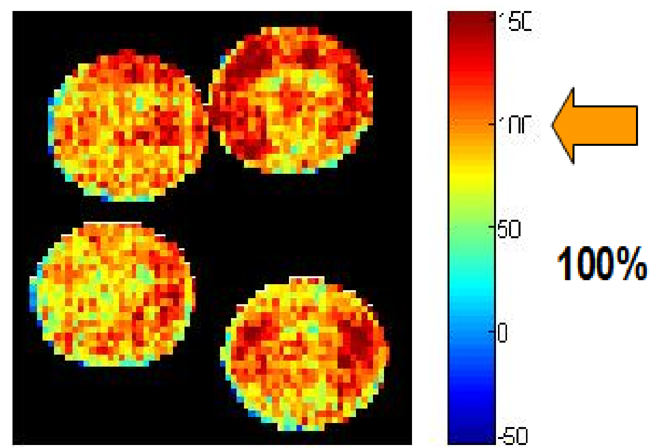
Novelties in instrumentation: Hyperspectral Imaging

Chemical imaging provides information about both composition and spatial features

Hyperspectral imaging is based on processing by means of chemometrics tools the reflectance spectrum in every point (pixel) of an image in order to visualize and quantify substances in 2D bodies.

It is more sensitive than conventional spectroscopy (1-pixel) because the spectral contribution of tiny bodies is concentrated in a few pixels.

HSI is particularly useful for detecting clots (homogeneity issues) and detection of persistent pollutant after cleaning processes (CIP validation).



Novelties in instrumentation: Time-gated Raman

A revolutionary fluorescence-free Raman system

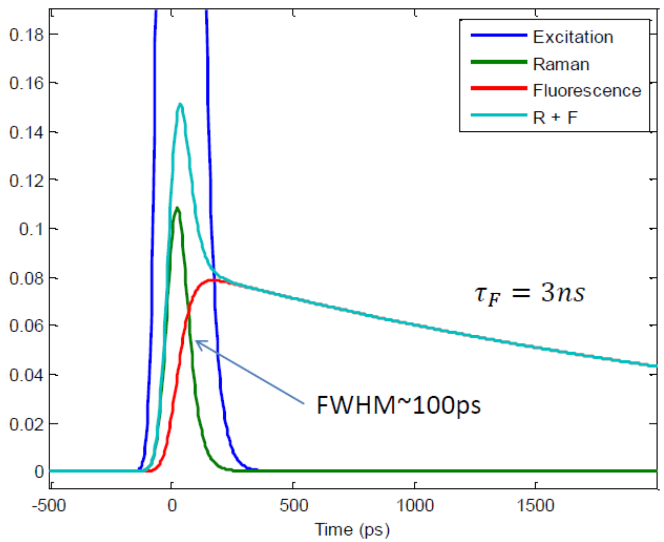
Concept: **Time-gated Raman** combines a novel ultrafast sensor with a fast pulsed chip laser in order to detect Raman effect before the unwanted fluorescence effect takes place.

Advantages:

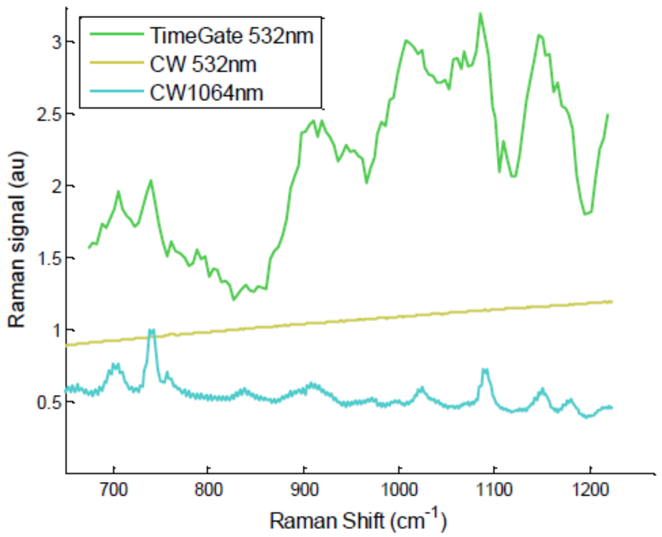
- Raman spectroscopy can be used **with almost any sample** because fluorescence is not an issue anymore
- Shorter wavelength excitation is possible which implies stronger Raman signals, therefore, **quantification** is now possible in the most of the cases
- The involved setup can be also used as a **time-resolved fluorescence spectrometer**; more information with the same instrument
- Much more **compact** (smaller) and **affordable** than equivalent alternatives. Easy to integrate for inline analysis

Novelties in instrumentation: Time-gated Raman

A revolutionary fluorescence-free Raman system



Raman effect takes place synchronously with the excitation pulse. However, the fluorescence signal reaches the maximum around 300 pS later and remains during long time. Hence, existing CW excitation systems cannot effectively remove fluorescence.



Amorphous indomethacin:
With conventional excitation (532 nm) the signal is purely due to fluorescence. By using 1064 nm excitation, fluorescence disappear but the Raman signal is to low. With time-gated Raman the signal is 3 times more intense and more spectral features can be seen.

The ProPAT Project

PAT as a strategic commitment in the European Union H2020 R&D Framework

ProPAT: “Robust and affordable process control technologies for improving standards and optimising industrial operations” aims to facilitate the adoption of PAT tools and the PAT philosophy in the Process Industries, including SMEs, by uniting the expertise generated over the last decades by top companies, universities and research institutions in Europe.

ProPAT involves the development of new affordable analytical probes and a Global Integration and Control Platform for implementing all the PAT grades (phases) in real-world specific applications for pharma, mining and chemical industries.

Horizon 2020

PROPAT INTEGRATED PROCESS CONTROL

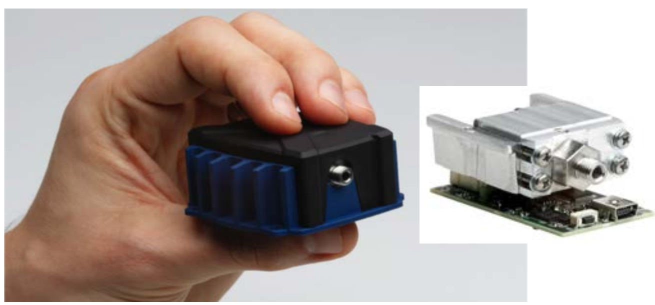
SPIRE Sustainable Process Industry through Resource and Energy Efficiency

The ProPAT Project

PAT as a strategic commitment in the European Union H2020 R&D Framework

Some figures and facts:

- Program: Horizon 2020's SPIRE
- 6 M€ budget
- 3 years -Kicked off on Jan 2015 in Brussels
- 16 partners: universities, institutes, large process industries (**GlaxoSmithKlein**...), SMEs... lead by IRIS
- 7 European countries



Compact and affordable online IR Spectrophotometer
(NIR-SWIR-MWIR-LWIR)
Spectral Engines (Finland)
MEMS-Fabry-Perot tunable filter

Compact and affordable online Particle Size Distribution analyzer
SixSenso/ICFO (Spain)
Scattering-based lensfree microscope

Process Intensification

A paradigm to build the tools for batch-to-continuous transition and boosting mini-factories

The original concept of **PI** was introduced in 1986 by Prof. Colin **Ramshaw** -who is considered the “father” of PI:

> “the physical **miniaturisation** of process equipment while retaining throughput and performance”

More recently, Stankiewicz provided a comprehensive definition:

> “PI involves the development of **innovative** apparatus and techniques that offer dramatic improvements in chemical manufacturing and processing, substantially decreasing equipment volume, energy consumption, or waste formation, and ultimately leading to cheaper, safer, sustainable technologies”

Process Intensification approaches

How could be a process intensified?

- **Innovative designs based on improving geometries or the way that the energy is supplied and removed:**
  - Enhanced acceleration by rotation, vibration or oscillation
  - Structured surfaces (grooves, fins, inserts...)
- **Radically novel technologies:**
  - Ultrasonication
  - UV (ultraviolet) radiation
  - MW (microwave) radiation
  - High static or dynamic electric fields
- **... and adding real-time in-line monitoring and control based on PAT philosophy to the intensified processors**

Adapted from a presentation delivered by Dr. K. Boodhoo (Newcastle University) in the IbD KO Meeting (Barcelona, 2015)

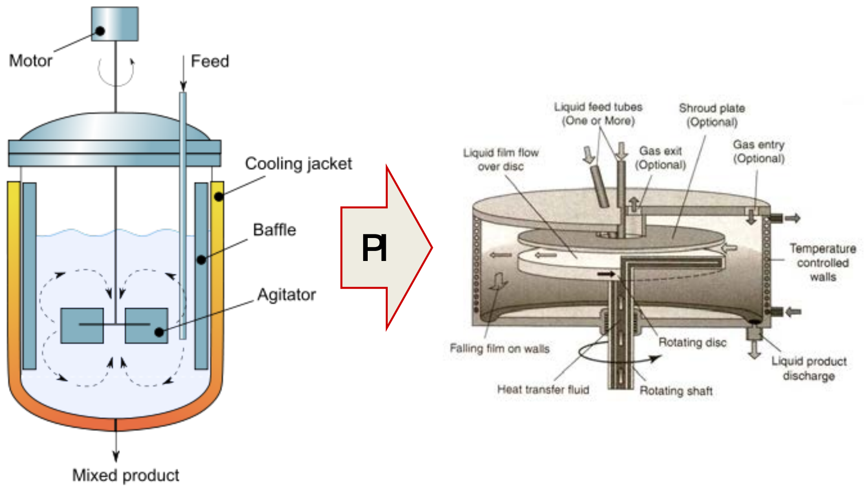
PI strategy

Goal: Designing a reactor where the process is only governed by its intrinsic kinetics

Matching…

- … **mass** transfer rate to rate of the key chemical reaction
- … **heat** transfer rate to exothermicity of reaction
- … **flow** behavior to ideal reaction scheme
- … **residence time** to optimum reaction time

Conventional system the process is affected by heat and mass transfer mixing and kinetics



In the intensified system the process is controlled only by reaction kinetics

Adapted from a presentation delivered by Dr. K. Boodhoo (Newcastle University) in the IbD KO Meeting (Barcelona, 2015)

Process Intensification drivers

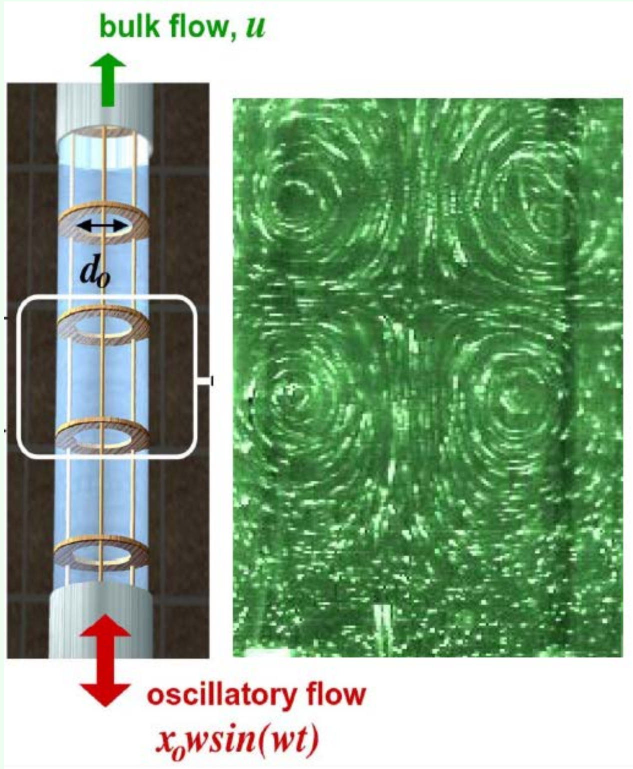
Why should we move to PI?

- **Environmental impacts:**
  - Reduced energy usage
  - Reduced waste
  - Better plant integration in the landscape
- **Process impacts:**
  - Higher yields
  - Safer processes
  - Improved selectivity (purity)
  - More controllable processes
- **Business impacts:**
  - Reduced OPEX
  - Smaller layouts
  - Flexibility (modularity)
  - Reduced time-to-market

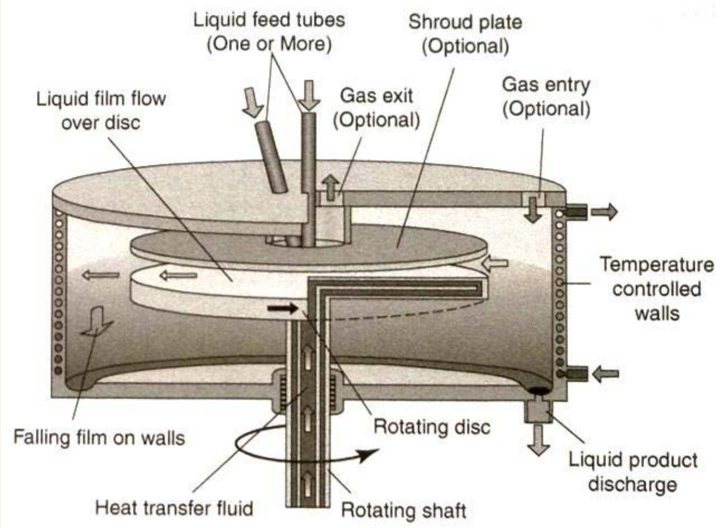
Some examples of PI technologies

Proven concepts that can be adapted to new challenges

OFR: Oscillatory Flow Reactor



SDR: Spinning Disk Reactor



Adapted from a presentation delivered by K. Boodhoo (Newcastle University) in the IbD KO Meeting (Barcelona, 2015) and "Process Intensification" 2nd Ed. D. Reay et al. Elsevier 2013

IbD (Intensified-by-Design) Project

PI as a strategic commitment in the European Union H2020 R&D Framework

IbD Project will develop a holistic **software platform** that will provide engineers with the knowledge, methodology and tools for the **design of Process Intensification devices and processes** based on a revolutionary ‘intensified-by-design approach’

Some figures and facts:

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- 10 M€ budget
- 3 years -Kicked off on Sep 2015
- 22 partners: universities, institutes, large process industries (**Sanofi, Almirall**…), SMEs… lead by IRIS
- 8 European countries

IbD Intensified by Design®

Horizon 2020

SPIRE Sustainable Process Industry through Resource and Energy Efficiency

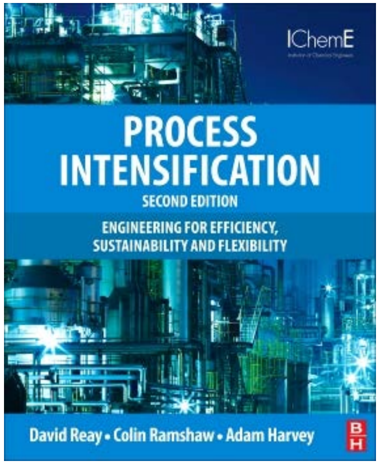
Process Intensification

The view of the pioneers: Prof David Reay contribution

Prof. **David Reay** and Prof. **Colin Ramshaw** are relevant PI pioneers who are actively participating in the IbD Project.

D. Reay manages David Reay & Associates, UK and is a Visiting Professor at Heriot-Watt University and Honorary Professor at Nottingham University. He is also Editor-in-Chief of Applied Thermal Engineering and author/co-author of 9 books related to heat exchangers and PI.

Colin Ramshaw conceived and developed the concept of PI in the 1980's while working for ICI. He is now a Visiting Professor at Cranfield University and a member of David Reay & Associates.



Summary

An invitation to share, improve and promote our vision on PAT and PI

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