

Overview of Process Analysis and PAT

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1.1 Introduction

Process analysis (PA) continues to be an evolving field across various sectors as is evident by its recent adoption within the pharmaceutical industry as an element of process analytical technology (PAT).¹ PA by definition is the application of ‘field’-deployable instrumentation (real-time analytics) and chemometrics for monitoring a chemical or physical attribute(s) (CQA) or detection of events that cannot be derived from conventional physical variables (temperature, pressure, flow, etc.). While PA is most often associated with the application of real-time analytics to production problems, the discipline can be considered to be much broader, encompassing sectors outside industrial manufacturing such as environmental, surveillance (chemical or biological agents, explosives, irritant, etc.) and hazmat consequence management. That is, the skills, techniques and instruments are applicable across a wide spectrum of real-time analytical problems. PAT is a broader field encompassing a set of tools and principles to enhance manufacturing process understanding and control (PUC) which includes process analysis, chemical engineering, chemometrics, knowledge and risk management, and process automation and control. Manufacturing quality by design (QbD) in part involves PAT strategies to reduce identified manufacturing risks that are associated with product quality.^{1,2}

Real-time differentiates process analysis from off-line laboratory techniques, where the former is on the timescale of seconds to minutes as opposed to hours or days. Furthermore, off-line approaches are often inadequate for root cause analysis in identify the process events that lead to off specification or poor product quality. The basic application of PA involves relative process trending or real-time monitoring (RTM) via the process instrument data stream (e.g., process spectral data). For example, various chemical reactions across industries (fine chemical, polymer, pharmaceutical, biochemical, etc.) can be monitored by *in situ* Fourier transform infrared–attenuated total reflectance (FTIR-ATR) spectroscopy where relative yet meaningful process ‘signatures’ are extracted via appropriate chemometric treatment.³ At a higher level, further process understanding is achieved by deriving relationships among multiple data streams including the process instrument data, engineering variables and analytical laboratory reference data. These deterministic

2 Process Analytical Technology

models provide real-time monitoring of product CQAs of interest and relationships to critical process parameters (CPPs). This level of process understanding affords a more specific control space definition, facilitates process control and process variance management or real-time assurance (RTA) of product quality. Product parametric real-time release (RTR) is the highest level of PAT where PA results (determinations, end points, etc.) replace conventional laboratory methods. All three levels, to varying degrees, provide a means to increase product quality (e.g., lower product scrap and rework), facilitate cost avoidance, increase production efficiency, reduce laboratory testing requirements and aid in identifying process improvement opportunities, all of which lead to reduced product manufacturing costs and risks.^{4,5}

Figure 1.1 depicts the hard and soft fundamentals of process analysis. First, the process instruments range from simple to sophisticated measurement technologies. The majority of process instruments are based upon electromagnetic radiation attenuation as evident by the techniques described herein. Further discussion on real-time instrumentation is provided in Section 1.3.

The next element is the process implementation approach involving either: (i) an in-line interface such as an *in situ* insertion probe (transmission, transmittance or reflectance), an optical flow cell or noninvasive sensors (e.g., acoustics); (ii) an on-line method where an autonomous sample conditioning system containing process instrument(s) is integrated to the process stream. These systems reduce the processing conditions (pressure, flow, etc.) that are suitable for *in situ* or integrated instruments and for appropriate measurement performance. They can also facilitate other analytical requirements such as sample dilution and reagent addition; or (iii) an at-line method where manually or autonomously acquired grab samples are measured with an offline instrument that is proximate to the process or process area as opposed to a remote quality assurance/control laboratory. Simple loss on drying instruments, FTIR or Raman spectrometers for material identification and sophisticated real-time high performance liquid chromatography (HPLC) or flow injection analysis (FIA) systems for QA determinations are examples of at-line approaches.⁶⁻⁹

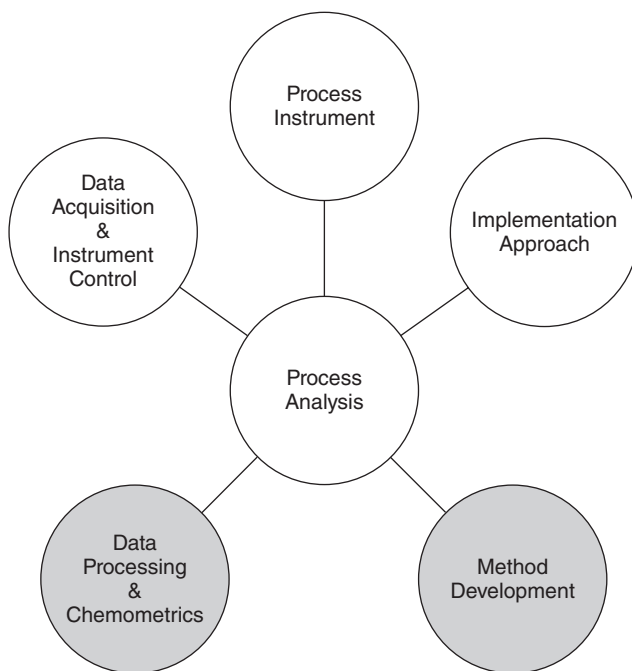


Figure 1.1 Hard and soft (gray) process analysis elements.

The data acquisition (DAQ) and instrument control element is an autonomous electronic system that provides several important capabilities including:

- data acquisition and archiving
- remote instrument control (i.e., measurement parameters)
- execution of real-time chemometric models
- instrument diagnostics and real-time measurement quality assurance.

Implementing this level of automation intelligence has been the most difficult to realize within manufacturing industries. That is, while automation controls integration of simple univariate instruments (e.g., a filter photometer) is seamless, it is much more problematic for multivariate or spectral instruments. This is due to the ‘tower of babble’ problem with various process spectroscopic instruments across process instrument manufactures. That is, the communications’ protocols, wavelength units and file formats are far from standardized across spectral instruments, even within a particular class of techniques such as vibrational spectroscopy. Several information technology (IT) and automation companies have recently attempted to develop commercialized solutions to address this complex problem, but the effectiveness of these solutions has yet to be determined and reported.

Data processing and chemometrics are methods for extracting useful information from the complex instrumental and other data stream(s) (see Chapter 12) for process understanding and the development of deterministic models for process control. The final element, the analytical method development life cycle, will be discussed further within this chapter.

PA applications are now found in various manufacturing industries such as chemical, petrochemical, agriculture and food, pharmaceutical and electronics, as well as service industries such as energy and utilities (e.g., water, sewage, etc.). While product quality and production efficiency are most often the objectives of PA, there are several attractive operational-type applications with substantial business benefits. These applications in general are simpler and have shorter development life cycles, often have lower financial risks, tend to require lower capital and staff resource investment, are wider in utility and easier to transfer across groups or sites. Real-time monitoring and control of industrial waste, site environmental monitoring, health and safety area monitoring and equipment cleaning verification are a few examples of operational-type applications.

It is indeed humbling to compose this introductory chapter as there is already a vast array of introductory literature on process analysis.^{10–13} It is worthwhile, however, to expand upon these works as the field continues to advance. This chapter is written from a PA experience base spanning three disparate sectors (chemical, pharmaceutical and surveillance) and various real-time analytical problems. The experience includes disparate products (fine chemical, polymer, pharmaceutical materials during product manufacture, etc.) and material physical states as well as PA solutions.

In this chapter I will provide a brief historic perspective, outline the manufacturing drivers for process analysis, provide a high-level overview of process analytical instrumentation, describe the PA method development life cycle prior to implementation and highlight the common pitfalls and challenges within the PA field. I have taken a pragmatic approach herein as the many benefits of PA are realized when a suitable process instrument and method is successfully implemented within a routine manufacturing environment, which is most often a multifaceted endeavor.

1.1.1 Historical perspective

Process analytics began nearly 70 years ago with a rich heritage within the petrochemical and chemical industries.⁷ The pilgrimage began in Germany where by the end of World War II their modern plants had

Table 1.1 *History of process analyzers*

Process analyzer technology	Adopted	Origin
Infrared photometers	1930s and 1940s	Refining
Paramagnetic oxygen sensors		
Thermal conductivity sensors		
Distillation-type analyzers		
Real-time gas chromatography ^a	1950s and 1960s	Chemical/petrochemical
On-stream fixed-filter UV-Vis photometry ^b		
Mass spectroscopy ^c	1970s	Chemical/petrochemical
Near-infrared spectroscopy	1980s	Chemical/petrochemical
Multicomponent UV-Vis filter photometry ^b		
Gas phase FTIR	1990s	Chemical/petrochemical
Mid-IR by ATR ^c		
On-line HPLC		
Process Raman	2000s	Chemical/petrochemical
Particle size instruments		

^aUnion Carbide, ^bDupont, ^cDow Chemical.

been extensively instrumented.¹⁴ In the two decades proceeding World War II, numerous refineries, petrochemical and nuclear plants were applying process analyzers world wide. In more recent decades, sophisticated process analyzers have become more commonplace across several sectors as summarized in Table 1.1. Today process analysis is mainstream within several manufacturing industries and in some cases is an integral component to process control.⁷

An introductory chapter would not be complete without highlighting the alternatives to PA: phenomenological and soft sensing approaches. The former is suitable for processes where the fundamental driving forces can be clearly identified and are generally understood, such as material transport and chemical reactor kinetics. For more complex processes, soft sensing can sometimes be effective in deriving a primary variable of interest from secondary variables. Soft sensing was first introduced by Joseph and Brosilow,¹⁵ and in recent years has been widely studied and applied for industrial process control. Soft sensing is preferred when the critical process variable or attribute is difficult or impossible to determine with a PA solution; product composition in a large distillation column is one such example. The selection of a phenomenological, soft sensing or a process analytical approach is based upon the required performance, implementation risks, routine operational factors and business considerations. For complex higher risk processes, a combination of these approaches (e.g., PA and soft sensing) is attractive as the convergence of independent methods ensures higher PUC assurance.

1.1.2 Business drivers

The goal of lean manufacturing and QbD is robust and efficient manufacturing processes that deliver consistent high quality product at the lowest possible cost where PAT is one route among several in achieving this goal. A fixed and variable costs of goods manufactured (COGM) matrix for a given factory (see Table 1.2) and associated process risk assessments to product quality (i.e., FMEA) provides the framework for identifying PA opportunities. The decision to launch identified PA projects should be carefully weighed

Table 1.2 *Process analysis by COGM*

COGM	Real-time process analysis application
Receiving	Input material QC/QA (e.g.,) identification
Manufacturing	Process end points Process fault detection Quality attributes trending (SPC or MSPC) Process control (feedback or feed forward)
Product release	Determination of final product quality attributes
Plant operations	Real-time water quality Cleaning verification Waste stream monitoring and control
Environmental health and safety	Hazardous area monitoring Environmental monitoring & compliance

QA, quality attributes; SPC/MSPC, statistical process control/multivariate statistical process control; CPPs, critical process parameters.

against the objectives and their probability of success as the workflow is often multifaceted and necessitates suitable resource as the next section describes.

1.2 Execution of Process Analysis Projects

1.2.1 Wisdoms

As we transcend from the information age to the age of ‘wisdom and knowledge’ as many modern philosophers suggest,¹⁶ it is perhaps fitting to offer the common ‘wisdoms’ within the field of PA.

- Sponsors often underestimate process analysis projects. Like any other project, PA projects necessitate appropriate staffing and capital resource as well as rigorous project management and leadership.
- While ‘turnkey’ process instruments are marketed, they (see hard elements in Figure 1.1) often require a degree of customization to realize the desired capabilities.
- Process analysis projects succeed or fail based on the degree of attention to detail and planning.¹¹
- A PA team should include experienced plant operators who are involved throughout the development life cycle. That is, plant operators have intimate daily knowledge of the manufacturing process and as such provide ‘real-life’ production experience that helps aid in developing the current process knowledge base that facilitates developing a suitable PA or PAT strategy. Moreover, they also often become the ‘plant champions’ and lead trainers and thus promote acceptance of the new process analytical system(s) during development and post commissioning. In addition, process instrument technicians or specialist are also key contributors to a PA team, particularly during the process instrumentation system specification and installation.
- Effective collaboration among the core four PA disciplines: analytical, chemometrics, process engineering and control automation along with other disciplines (e.g., pharmacist, chemist, analyst, product formulators, etc.) is imperative to realize effective PAT solutions that are consistent with the intended lean manufacturing or QbD objectives.

- A common theme among stakeholders is the significant and sometimes surprising process knowledge that is realized upon implementing a PA solution. PA can demonstrate that a given process is not as well understood or robust as previously assumed by phenomenological principles, soft sensing approaches or as determined by conventional means such as off-line laboratory verification testing methods.
- Installation of a real-time instrument and associated method is not always the goal or outcome of a PA project. Most PA projects can be deemed successful on the basis of the significant increased process understanding that is achieved during the development life cycle.
- A real-time process instrument can either be implemented in routine production or be used as a reachback capability for diagnostic purposes during adverse production events.

1.2.2 Team structure

Process analytical projects are most often part of an overriding project such as new product or product line extension development, or continuous improvement initiatives, both of which often involve large multidisciplinary teams. Often a PA or PAT subteam is sanctioned by this wider body to develop the process understanding and control required to deliver consistent product quality and optimal process efficiency. While various organizations construct PA teams differently based on their operating model, Table 1.3 describes the various PA contributors required and the matrix teams that often emerge during the project life cycle. A core group within the PA subteam often drives the project which includes a project manager, a process analytical chemist (PAC), a product/production specialist and a process engineer.

1.2.3 Project life cycle

While Chapter 2 outlines the implementation of PA solutions, it is appropriate to augment this discussion to highlight several prerequisite development steps. Figure 1.2 is a high-level framework for developing a process analytical solution.^{17–19} The project initiation phase involves project definition and scoping. The former entails specifying the project problem statement, defining the project goal and outlining the objectives. It also includes a strategic and tactical development plan, a high-level project time line and the required

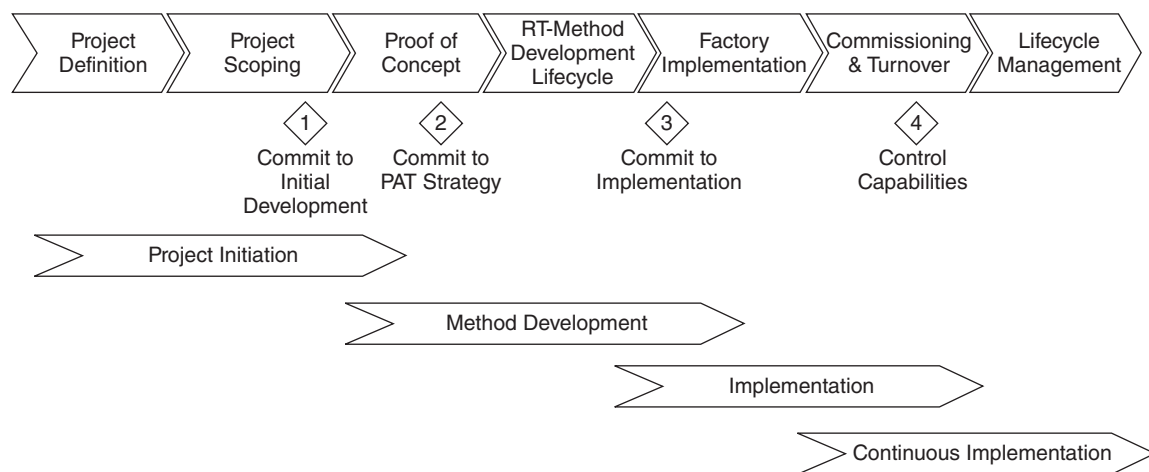


Figure 1.2 *Process analytical method development life cycle.*

Table 1.3 Typical process analytical contributors

Matrix team	Contributor	Roles
Project management	Project manager	Project management Capital management Sponsor(s) and stakeholder communications
	Operational excellence expert	Business justification Project metrics Facilitate effective use of lean sigma tools
Analytical matrix team	Process analytical chemist ^a	Process instrumentation selection and specification Process instrument qualification and validation Process analytical method development Analytical Merits and method equivalence Process instrument operation and training Instrument measurement optimization
	Chemometrician	Data management and data fusion Process data analysis Multivariate data analysis Analyzer calibration model development Method equivalence Process models development (e.g., MSPC) Experimental design (e.g., DOE)
	Analytical chemist (analyst)	Reference method selection Reference method capabilities Method equivalence
	Product/production specialist	Product formulation Process steps Input materials and their characteristics
	Process engineer	In-line/On-line analyzer integration Process understanding (IPOs, P and IDs, etc.) Facilitate risk assessments Process understanding Process Instrument integration
	Production engineer	Process observations and geology Manufacturing scheduling Coordinates development within production Validation and change control management Operations
Process engineering	Automation controls	Equipment automation Implementation of control strategies
	Manufacturing representative (e.g., customer)	Production and operational logistics Scheduling and change control Training and SOPs
Production	Plant operations manager	Operator community buy-in Training
	Production engineer	Production experience Operator community buy-in
	Lead operator	
	Process instrument technician/specialist	

resources such as capital costs and staffing. The scoping step is aimed at collecting process details (i.e., engineering walkthroughs), defining analytical requirements (see Section 1.2.4) and developing an understanding of the manufacturing process. The latter includes understanding the process steps, historic trending, mapping the known and potential sources of variance that contribute to the process capability (C_{pk}), accessing existing analytical methods and other knowledge gathering activities such as information about material characteristics and material processing behaviors. This forms the current process knowledge base to develop a suitable PA strategy or PAT strategies. It may also result in realizing a viable simpler solution where existing capabilities could be utilized (e.g., a process engineering solution) rather than developing a new PA approach.

The proof of concept (PoC) step entails accessing various suitable real-time PA techniques which includes instrument capabilities, merits of implementation (i.e., in-line, on-line or at-line) and their viability within a routine manufacturing environment (e.g., robustness, operational complexity, longevity, etc.). It is often useful to determine the maturity of each process instrumental system under consideration, both within the organization and the process instrument marketplace, as it aids in determining the project workflow. That is, a nonstandard, new or novel process instrument is a complex workflow as it involves a significant validation workload, original method development, higher risks and longer time lines. However, the drawbacks of a nonstandard approach should not be the overriding determinant. That is, the common engineering practice of instrumental standardization within large corporations can become an Achilles' heel. While there are sound rationales for standardization such as validation transference, deployment efficiencies (training, procedures, etc.) and regulatory acceptance, limiting the analytical capabilities to specific instrument standards compromises the innovation required to address various process analytical problems. The same applies in over standardization with a particular process analytical technique such as near infrared (NIR).

Initial PoC activities are often at the bench scale where the general process instrument analytical capabilities are determined across several real-time targeted analytical techniques (e.g., NIR, Raman, UV-vis, etc.). If a particular technique has already been determined, it is also worthwhile to evaluate various instrumental variants (e.g., NIR types such as interferometric, monochromatic, filter photometer, etc.) during this phase. The bench-level investigations are facilitated with either process grab samples or laboratory-prepared surrogate samples. Process samples are preferred provided the process is variable enough to demonstrate measurement capabilities (i.e., accuracy, precision, sensitivity, etc.) across the CQA range of interest (e.g., concentration range). Once the assessment is complete an instrument is selected. The selection is based on the analytical performance and practical considerations such as instrument cost, size, integration and operation complexities, cost of ownership and instrument-to-instrument performance. This information is correlated via a measurement system analysis (MSA) to provide the cohesive knowledge required for the second decision gate.^{20,21}

Following the bench studies a project team meeting with key team members and the sponsor(s) is often held to review the analytical data and business case to determine the merits of committing to the piloting stage. Transitioning from the bench to a pilot environment often necessitates capital investment and staff resource to procure the selected process instrument, modify manufacturing equipment and facilitate other change management activities (e.g., compliance, operating procedures, etc.) and thus is an important business decision. The objective of the process analysis piloting step is fourfold:

- determination of the actual process measurement capabilities (sensitivity, accuracy, repeatability and reproducibility, etc.) within the intended real-time application
- optimization of the measurement performance
- developing process understanding to determine the knowledge and control space
- developing required chemometric models and
- evaluating proposed process control strategies

Additional piloting activities include calibration model optimization and verification, determining instrumental robustness (i.e., MTBF) and method and equipment validation. The pilot PoC concludes by revising the MSA as required, completing the business case²² and reconciling the method performance against the *a priori* acceptance criteria as prerequisites for the pivotal implementation decision gate. Once a PA solution is deemed 'fit for purpose' and the business case ratified, the project moves to the implementation stage as discussed in Chapter 2.

1.2.4 Project scoping

The project scoping provides the framework for selecting a suitable technique, defining the method and its implementation. Generic data sheets are helpful for capturing the information required for formulating the PA development approach.²³ Often these data sheets are working documents throughout the PA project lifecycle. The following list provides the common elements:

Project management

1. Project goal, objectives, timeline and milestones
2. Technical and business rationales: (increase process robustness, process efficiency, improved quality, cost reduction, etc.)
3. Cost considerations

Process engineering

4. Process description (equipment, materials, process steps, etc.)
5. Normal process conditions (temperature, flow, pressure, etc.)
6. Process startup and shutdown effects on product quality
7. Current and desired process capability (C_p)
8. SPC or MSPC review:
 - a. process upsets and when they occur
 - b. process genealogy
 - c. common trends and relationships
9. What is the current process control strategy?
10. Engineering walk through:
 - a. process and instrument diagram (P&ID) verification or redlining
 - b. determine suitable process analysis monitoring points
11. Define PA constraints
 - a. What is the desired PA approach (i.e., in-line, on-line or at-line)?
 - b. Define in-line or on-line process or mechanical constraints (e.g., insertion probe size, penetration depth, location, etc.)?
 - c. Process instrument limitations (e.g., size, supporting utilities, safety, communications, etc.)

Analytical

12. What is the measurement intent: determining a quality attribute, detecting a process event (end point or fault), etc.?
13. What are the current off-line analytical methods and process analytical approaches?
 - a. Define the performance of these methods (accuracy and precision, speed, sensitivity, etc.)
 - b. Can they be further optimized?
 - c. Can an accepted off-line method be converted to a real-time method?

14. Define the method equivalence criteria or acceptance criteria.
15. What are the analytical requirements of the real-time method? (Accuracy and precision, range, speed, sensitivity, etc.)
16. What are the attributes of interest? How many? What are their ranges?
17. Define other analytical details (i.e., sample matrix, sample state, potential interferants, etc.)?
18. What is the current grab sampling approach?
 - a. Frequency, sample size, chain of custody, etc.
 - b. Is it a suitable protocol for PA method development (e.g., calibration; see Chapter 3 on sampling)
 - c. Is the sampling approach representative of the process?

Operational and automation controls²⁴

19. What are the criteria for instrument automation control and data acquisition?
20. Is the PA method used in tandem with other real-time control solutions (e.g., process engineering)?
21. What are the measurement assurance metrics (health, status and diagnostics)?
22. Define the data storage requirements
23. What type of reported real-time result(s) is desired? (e.g., quantitative value, pass/fail, etc.)

Other

24. What is the area classification?
25. What are the validation criteria and when is it required?
26. Define the technology transfer team. Who is the system owner? Who will operate and maintain the PA system? Who are the reachback technical experts post commissioning?

1.2.5 Common challenges and pitfalls

While throughout this chapter various challenges and pitfalls have already been discussed, this section provides the additional common difficulties in realizing a PA solution within routine production. In general PA requirements far exceed laboratory-based analytical methods, even for the simplest of applications. That is, a successfully implemented process analytical solution provides reliable quality data while withstanding the routine factory operational conditions (environmental, work practices, etc.). It also functions with negligible operator and expert intervention. Based on this definition a PA solution necessitates:

- robust process instrumentation with suitable analytical merits
- optimized process integration and operation
- robust chemometric models or data processing algorithms
- representative process data over time and conditions
- autonomous process instrument control and data acquisition
- real-time measurement assurance (i.e., smart sensing)²⁵
- suitable information technology and automation controls infrastructure for efficient data fusion and archive management
- sufficient method development, validation and ongoing compliance
- suitable instrument validation and compliance

- a comprehensive onsite process instrument program (metrology, instrument maintenance, training, sufficient on site instrument specialist, etc.)
- identified performance metrics and continuous improvement plans

Inappropriate selection of a suitable process instrument is the most common pitfall hence the focus within this chapter and the literature.^{17–19} That is, piloting of various process instruments, including current or accepted PA solutions, is an important PoC activity as it forms the technical basis in selecting an appropriate process instrument. Insufficient process interfacing is also a common pitfall, in particular for in-line approaches. For example, in-line probe location, its angle of insertion and penetration depth requires sufficient investigation to realize superior measurement performance and minimal process impact. Often this is a challenge, as it may require the evaluation of various mechanical interface designs and process equipment modifications. This is more problematic within regulated industries where the resistance to change is much higher, in particular in modifying validated manufacturing equipment. Finally, instituting effective operator training, maintenance and continuous improvement programs during commissioning is yet another common pitfall. This justifies including targeted plant operators and other key plant staff during the PA development life cycle as it greatly aides with these change management activities.

Likewise there are four common challenges. First, capturing sufficient and suitable process understanding development data is often a daunting effort. Many routine processes under normal operating conditions, in particular continuous manufacturing processes, are inefficient in providing the data characteristics required for PA method development. That is, many routine manufacturing processes, once in a state of control, do not vary enough on a routine basis to meet the requirements for PA method development. The criteria for robust empirical chemometric calibration models for example necessitate capturing representative process variability spanning the concentration range of interest and a significant volume of data across particular process conditions. Moreover, deliberate changing manufacturing conditions (e.g., during designed experiments) for process understanding purposes that often produce scrap product are often not a viable option, particularly in the chemical or equivalent industry where the financial margins are often very competitive. Thus, when empirical models are required, the state of the manufacturing process over time determines the rate of progression of the PA method development life cycle. Known seasonal effects further confound this problem. This representative process data problem in particular often necessitates sound technical leadership to manage stakeholder expectations.

Collecting high quality process data and knowledge is also a challenge. While this may be considered a trivial detail for practitioners, orchestrating effective process data collection is a significant team effort as it includes various multifaceted data streams (process instrumental data, engineering variables and reference laboratory data) and disparate groups, often across geographic locations. It also includes data management and fusion, a suitable practical grab sampling protocol and sufficient logging of observed process events that are imperative for developing empirical PAT models. Again, process analysis projects succeed or fail based on the degree of attention to detail and planning.¹¹ In other words, process manufacturing science necessitates the utmost adherence to the sound scientific practices, effective management and cohesive teams to realize robust PA methods and useful process understanding knowledge to realize effective process quality control.

Unrealistic sponsor expectation is the next common challenge for PA projects. That is, sponsors often treat PA projects analogous to conventional plant engineering upgrades or modifications where rapid return on investment is often expected. Managing expectations throughout a development life cycle is an important element to project success, particularly given the often encountered challenges discussed herein.¹¹ Finally, PA teams are often comprised of cross-organization members from both research and development (R&D) and manufacturing site(s). While on first inspection this may seem minor, these disparate organizations,

irrespective of the industrial sector, may have widely disparate change management procedures, capital project processes, equipment, engineering standards and data management practices. Moreover, the PA requirements between R&D and at a routine manufacturing site are often not mutually exclusive. That is, R&D necessitates versatile process instrumentation to address the diverse analytical problems encountered within product development. In contrast, factories require robust and automated process instrumental solutions. These differences illustrate the need for effective technology transfer.

1.3 Process Instrumentation

Process instruments are grouped into four categories.⁷ Physical property analyzers are the most common, which monitor a physical attribute such as refractive index, thermal conductivity and viscosity. Electrochemical analyzers monitor the voltage or current produced from an electrochemical cell which is related to solute concentration. Examples include conductivity, pH, redox, and trace oxygen analyzers. Combustion analyzers monitor one or more species in a gas or liquid process stream. And spectroscopic, process spectrometers and spectrophotometers, monitor an attribute via electromagnetic interactions (absorbance, emission, scattering, etc.) with the process sample. PA discussed within this treatise fit within this latter category. A thorough treatise of PA instrumentation covering these four categories can be found elsewhere.^{7,13,26}

1.3.1 Process instrumentation types

In general terms, process instrumentation fit within two broad categories: analyzers and sensors. Analyzers by definition are large or bulky instrumental ‘systems’ (e.g., 19-inch rack mountable systems), that necessitate fixed installation, various external utilities (power, plant air, etc.), routing of high cost fiber optics (spectral quality) or cabling from the analyzer to the probe or flow cell and space planning. In contrast, sensors are compact, lightweight and self-contained devices with most of supporting utilities onboard. Small ‘handheld’ photometers and spectrometers are examples of sensors for PA.^{27,28} From a cost perspective analyzers range from \$50k to 200k whereas sensors are between \$20 to 100k. Sensors tend to be more attractive solutions as they are often much more robust, lower cost, simpler to integrate, easier to maintain and operate, mobile and are suitable for distributed deployment across a manufacturing line or plant. Most current commercial process spectroscopic instruments reside within the analyzer category.

Figure 1.3 depicts a high-level comparison among common process instruments based on ‘analytical’ and ‘business’ criteria. The former is a continuum between instrument detection performance (i.e., sensitivity, quantification limits, speed, precision, etc.) and selectivity. The business dimension attempts to quantify the implementation complexities and cost which includes: capital cost, cost of ownership, training, maintenance and implementation and routine operational requirements. While the composite score of each process instrument along these two dimensions may be argued among expert practitioners, the resultant plot would nevertheless highlight the wide disparity among process instruments in terms of their analytical performance and operational-implementation complexities.

1.3.2 Novel process instrumentation

While spectral ‘analyzers systems’ as described above have served their purpose for several decades as process instrumental solutions, today’s complex problems and environments necessitate practical and sophisticated sensors or similar compact process instruments. The electronic revolution over the last several decades has resulted in numerous microelectro-optical devices such as cell phones, PDAs and iPods. These

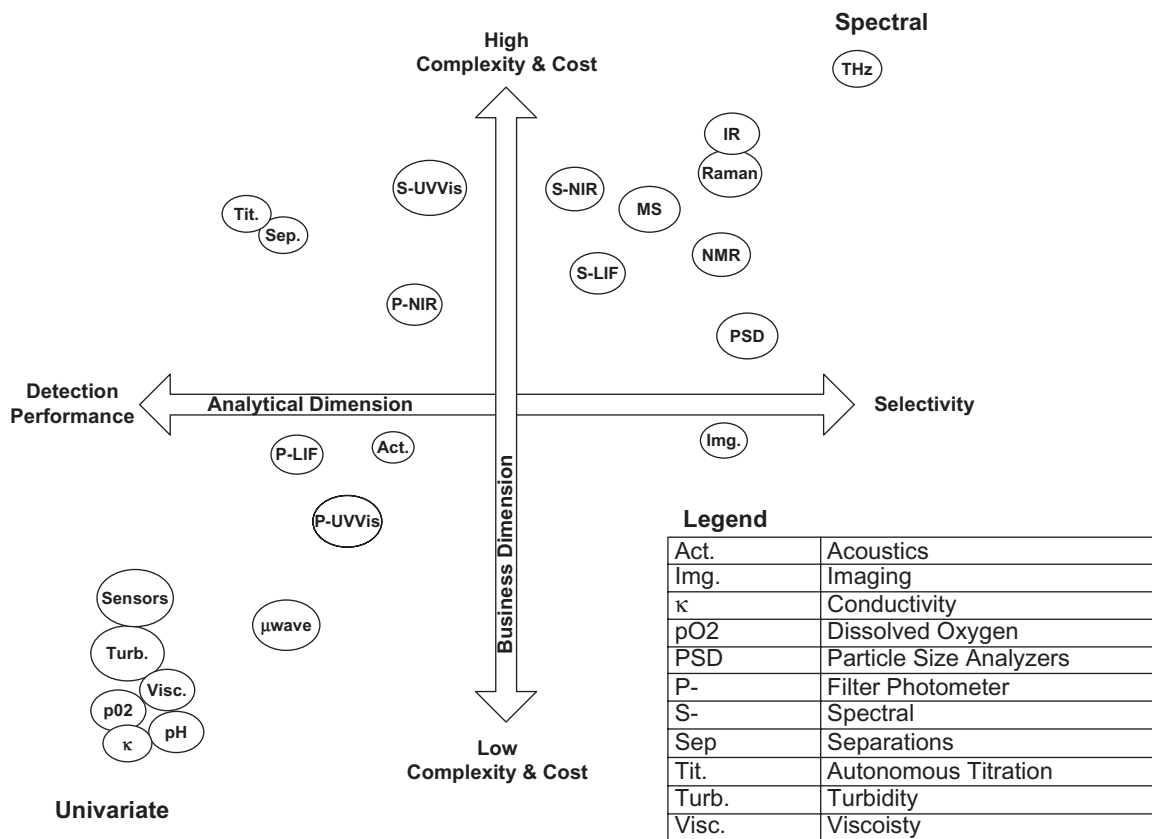


Figure 1.3 Process instruments classification.

advances along with other microfabricated capabilities afford the OEM underpinnings for spectral sensors that are beginning to appear on the marketplace.^{29–32} Micro-electromechanical systems (MEMS)-based NIR spectrometers and LED sensors²⁷ are prime examples of modern in-line or on-line process optical sensor technologies.^{30,31}

1.4 Conclusions

A fit for purpose process analytical solution provides the analytical and automation capabilities for reliable monitoring of product quality attribute(s) in real-time or process events detection while withstanding the routine factory operational conditions. It also affords smart sensing features to ensure a high degree of measurement assurance for defensible performance that is required for real-time manufacturing control. This introductory chapter has attempted to introduce the multifaceted aspects of process analysis and the complexities involved in realizing a real-time process analytical solution within routine production. The diversity of analytical problems, the depth of knowledge and rigor required is the essence of this rewarding field to process scientists and engineers.

1.5 Glossary of Acronyms and Terms

Analyzer	A large instrumental system (e.g., 19-inch rack mountable system) that necessitate a fixed installation, various external utilities (power, plant air, etc.), routing of high cost fiber optics or cabling and space planning.
COGM	costs of goods manufactured
CQA	Critical quality attribute
DAQ	data acquisition
DCS	distributed control system
FMEA	failure mode and effects analysis
IT	information technology
MSA	measurement system analysis
MTBF	mean-time between failures
PA	process analytics
PAT	process analytical technology
PoC	proof of concept
PUC	process understanding and control
QA/QC	quality assurance/quality control
QbD	quality by design
RTA	real-time assurance
RTM	real-time monitoring
Sensor	Compact, lightweight and self-contained instrument with most of supporting utilities onboard

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