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SST

SAMPLING SCIENCE & TECHNOLOGY

Introduction to "Process Analytical Technology" (PAT)

for the Sampling Community

The Role of TOS in the PAT Revolution
From Mining to Pharma Manufacturing

PAT for Conveyed Flows
Representative Real Time Measurement

Chemometrics for PAT
An Introduction for Samplers

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PAT: Something Completely Different

By Kim H. Esbensen (Editor)

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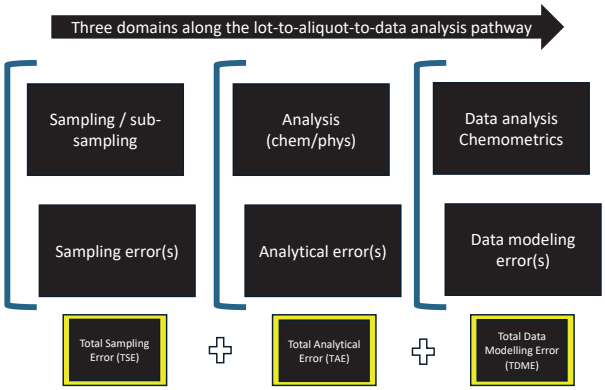
The scope for this issue is 'Sampling for PAT'. For a very large proportion of traditional samplers and a great many readers of SST the term PAT is undoubtedly rather unknown. For this reason, SST has commissioned two educational lead-in feature articles 1) "What is PAT?" and 2) "The inspiring role of TOS in the PAT revolution in pharma". These articles present authoritative introductions and descriptions of applied Process Analytical Technology (PAT) with scopes that aim and prepare for generalisation: While having had a tremendous impact in the pharmaceutical industrial sector for three-four decades, PAT has simultaneously transgressed way outside its own borders. Perhaps without having made a great splash in the world sampling community, there actually have appeared several recent forays making use of selected aspects of PAT (WCSB10, 11), but these have lacked a structured theoretical underpinning. This is addressed heads on by the third article, "The Fundamental Sampling Principle for PAT".

For quite some years it has been a wish of the editor to present to the sampling community a more diverse introduction to PAT: scope, concept, design, implementation, usages and application experiences, which was finally realised with a broad solicitation. Six very experienced experts responded positively. Thus, in this issue some very inspiring accounts of the current interface between TOS and PAT can be found. All hail to HK, HM, DK, BS, RR and GR. I hope you will enjoy reading this multi-faceted collection of reflections and experiences from this distinguished line-up of practitioners, scientists and technology developers, academic and commercial both. It is hoped the present compendium will create a platform and will inspire to further PAT developments in the sampling realm. There are undoubtedly great potential benefits to be reaped as the possibilities for Process Analytical Technologies are put into practice – but it is also necessary to express serious warnings. Successful PAT applications are far from the all-too-simplistic idea of sticking a sensor into the process stream. The sampling community can learn a very great deal from this issue!

Then there is the domain of analysis *sensu stricto*. For want of space it has been decided not to go into this immense domain in this issue (plenty of opportunity if/when need be).

There is also a third domain on the *other side* of analysis, the domain of spectral data analysis and modelling, which must be viewed in its proper three-domain data quality context: Sampling / Analysis / Data modelling:



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Three successive domains are involved to cover the full 'lot-to-analysis-to-DSR' pathway.

To at least try to create a picture within the borders of the full canvas, this issue brings an article sketching the critical data modelling needed in this domain: multivariate data analysis. Here the reader gets a compact introduction to **why** and **how** *chemometrics* has played an essential role for PAT's success in the last 3-4-5 decades.

Finally, as is by now a well-established tradition in SST, this issue also contains an installment of Alan Rawle's scholarly series "Giants in Sampling", this time on Robert H. Richards. And any SST issue would not be complete without an updated announcement on the status of the next World Conference on Sampling and Blending, which is WCSB12 (2026): **where?, when?, how?**

Enjoy your reading.

Introduction to 'Process Analytical Technology' (PAT) for the Sampling Community

By Gary E. Richie[1]

DOI: 10.62178/sst.004.002

ABSTRACT

The evolution of Process Analytical Technology (PAT) from its roots in Process Analytical Chemistry (PAC) to its current integration with the Theory of Sampling (TOS) marks a pivotal transformation in pharmaceutical manufacturing. This article traces the historical, technical, and regulatory milestones that have shaped PAT into a comprehensive framework for ensuring product quality through real-time process understanding and control. It is also significant, and highly beneficial for society, that the modern PAT concept/framework has been found to be applicable in many other industry sectors.

At the heart of this transformation lies the recognition that sampling is not merely a preparatory step but is in fact a critical determinant of analytical reliability. The incorporation of TOS principles, particularly the concepts of material heterogeneity, lot dimensionality, Total Sampling Error (TSE) and sampling process supremacy with regard to representativity, has elevated the role of sampling from being viewed as a procedural necessity to a scientifically governed critical discipline. The key to its adoption by regulators and industry is the implementation of control strategies for materials, sampling equipment (hardware and software), methods, training, and lifecycle management. When combined with chemometric modeling and multivariate calibration, TOS and PAT becomes powerful enablers of Quality by Design (QbD), continuous manufacturing (CM), and lifecycle management.

Regulatory guidance from the Food and Drug Administration (FDA), International Council for Harmonisation (ICH), and international standardization bodies now reflect this integrated perspective, emphasizing the need for representative sampling, robust analytical procedures, and risk-based process validation. The convergence of PAC, PAT, and TOS provides a unique, powerful *unified strategy* for minimizing uncertainty, maximizing process efficiency, and ensuring regulatory compliance across the pharmaceutical product lifecycle.

As the involved industries move forward, the continued refinement of sampling strategies, sensor technologies, and data analytics will continue to be essential. The future of PAT lies not only in further technological innovation but in the disciplined application of scientific principles that *bridge* the gap between relevant, optimized measurement (sampling-*and*-measurement) and meaning—between critical data and optimal decision-making. This article also presents a first, hopefully inspiring, scope of potential further PAT impact(s) in industry sectors that already rely on TOS.

1. Introduction

This article introduces the concept of Process Analytical Technology (PAT), with underpinnings from analytical chemistry, signal processing, process engineering, along with developments from computer science, mathematical, statistical and multivariate sciences, and considerations for necessary reference samples needed for calibrations.

In 1989, Harald Martens and Tormod Næs published a pioneering book *Multivariate Calibration*. Although the book's primary focus was on what we today refer to as chemometric data analysis and modeling — aka "soft modeling", a subject that will be discussed briefly later in article, the authors also comment on an aspect of data modeling that is useful for here, with regard to connecting and relating process characterization with first principles of acquiring relevant calibration and validation samples.

1 Equipment Validation Engineer, Actalent

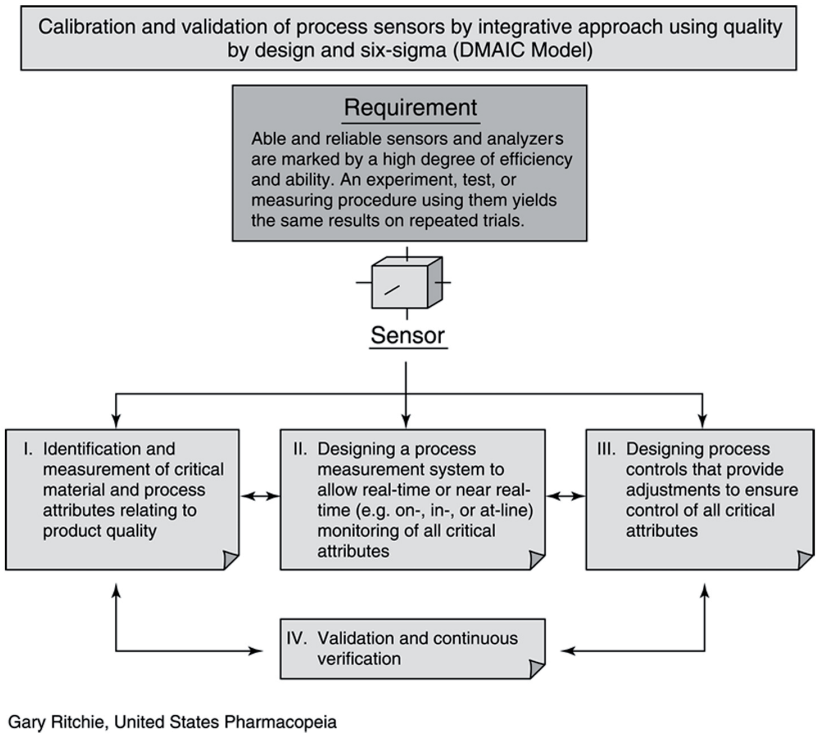


Figure 1: Integration of calibrations and validation, DoE and QbD considerations of process sensors.

They emphasized that there are critical conditions necessary for converting sensor data into reliable analytical results leading to process knowledge. To quote Martens and Næs (1989):

The same holds true for process sensors. It will be shown that, through transduction and transmission of signal into impulse, or through calculation into a determined value, the flow of process data into process information, which then may be transformed into process knowledge, can be turned into useful process understanding only if:

a) *the knowledge behind the sensor systems intended application can be shown to be valid*
b) *the quality of the data is accurately and precisely verifiable when that information is needed*
c) *is based on appropriate measuring reference systems*

A further condition that is necessary is that the system must be adjustable (preferably in real or near-real time).

The requirement that process sensors (Figure 1) must be able and reliable, and give consistent and repeatable results is a cornerstone of PAT that has evolved out of an integrative approach from QbD, DoE, and quality management system principles (Dziki et al., 2004).

Thirty-six years later, it is now obvious that another important factor can also be shown to be critical for the uncertainty of the analytical result obtained from the raw data of a process, that being the *process sampling* procedure itself (Esbensen, 2025). It is fair to say that Martens, Næs and many others who pioneered the use of process analysis focused mainly on what came *after* the sampling step; trying to understand how the raw data (spectral) properties impact modelling characteristics (linear, non-linear) and prediction behaviors. However, with the realization that must now be regarded as very firmly established, the following must be considered with respect to sampling in process analysis (DS-3077, 2024; Esbensen, 2000; Esbensen, 2025):

1. There are significant error effects (leading to uncertainty contribution) originating from inadequate (non-representative) sampling of heterogeneous materials (the domain of TOS).
2. The objective is to achieve representative process sampling (the domain of TOS).
3. Ensure valid analytical data quality assurance (the domain of PAT).

With the foundational concept of the Total Sampling Error (TSE), analytical results can now be considered complete with respect to uncertainty arising from both what comes *before* analysis (Esbensen, 2020; Esbensen, 2025) and from what comes *after* sampling, the traditional Total Analytical Error (TAE).

Just as the practitioners of process analytics in pharmaceutical manufacturing now have guidance from TOS principles in evaluating analytical results obtained from Process Analytical Technology (PAT) (Romanach, 2025), the analysts too could greatly benefit by investing an effort to understand that beside analytical uncertainty, there are other error sources that contribute to the overall uncertainty of an analytical result. Today, these sources are well characterized and understood throughout the history of the development of process analysis and other disciplines.

Presented below is a condensed version of the historical developments of PAT. The rest of this article will explore key highlights from process analysis' early beginnings, to the pivotal launch of Process Analytical Chemistry (PAC), initially funded by the National Science Foundation (NSF) in the USA, later implementation in pharmaceutical manufacturing from the FDA (Food and Drug Administration, 2004b), a core component of their 21st century Current Good Manufacturing Practice (CGMP) Initiative, and on through to the current era of ICH guidance development and adoption to the integration of TOS for Continuous Manufacturing (CM).

2. Background

Process analysis has its beginnings from its development in industrial engineering and analytical chemistry (Baugmann, 2005; Center for Process Analytical Chemistry, 1984a, 1984b; Callis et al., 1987). Baughman (2005) provides a historical perspective of PAC (Process Analytical Chemistry) from its early introduction in oil (crude) processing and in petrochemical (refined) manufacturing, to the development and application of instrumentation for the near real and real-time measurement and analysis of manufacturing processes. Later works by Callis, Illman, and Kowalski, associated with the establishment of the Center of Process Analytical Chemistry (CPAC) at the University of Washington, Seattle, and Layloff, Hussain, Afnan, and Watts, for ushering in Process Analytical Technology (PAT) initiative at the Food and Drug Administration (FDA), and many others, provides a firm footing for future progress of process analytical chemistry and technologies.

For the purposes of this article, interest in Process Analytical Chemistry & Technology (PCA&T) is primarily focused on the quality of the analytical result and on the critical role of all three domains: TOS, analysis and chemometrics (multivariate data analysis and – modeling).

Traditionally, an analytical result has been thought of consisting of two parts, a value (the determined concentration of the analyte) and an uncertainty component arising from the measurement itself.

TRADITIONAL ANALYTICAL RESULT

$$\text{Analytical Result} = \text{Value} + \underbrace{\text{Uncertainty } (MU_{ANAL})}_{\text{MEASUREMENT UNCERTAINTY } (MU_{ANAL})}$$

The measurement is typically a single end point measurement, but in the case of process streams, could also reflect a continuous measurement. The Measurement Uncertainty (MUANAL) reflects an error to the measured value stemming exclusively from the analytical method, the Total Analytical Error (TAE). The numerical value is the true, or accepted value of a quantity.

Following the comprehensive understanding presented by the Theory of Sampling (TOS) (Danish Standards, 2024; Esbensen, 2020; Esbensen, 2025), it is necessary to *augment* this understanding, by including the Total Sampling Error (TSE). Thus, the total, effective Measurement Uncertainty (MU_{TOTAL}) associated with a process analytical result is today understood as comprised by two components, one originating with sampling (TSE), the other associated with the analytical method (TAE). These two errors manifest themselves as additive MU components:

REVISED ANALYTICAL RESULT

$$\text{Analytical Result} = \text{Value} + \underbrace{MU_{SAMP} + MU_{ANAL}}_{\text{SAMPLING + MEASUREMENT}}$$

3. Process Analytical Chemistry (PAC)

PAC is described as originating from five alternative analytical interactions with a process, which is often envisaged as a material stream in a pipeline: Measurement setups can be *off-line*, *at-line*, *on-line*, *in-line*, or can be *non-invasive* analysis. These concepts stem from having the focus on the way (mode) of a PAT probe (sensor) is *interacting* with the process stream in order to obtain a measurement.

Table 1: Process Sampling Modes.

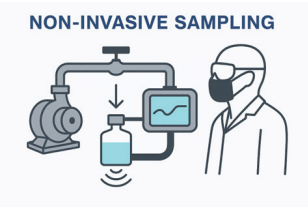
Analysis Mode	Sampling Mode	Example
Off-Line	Manual removal of the sample and transport to the measuring instrument.	
At-Line	Manual removal of the sample and transport to the measuring instrument, installed in close proximity to the process line.	
On-Line	An automated sampling system is used to extract the sample, condition it, and present it to an analytical instrument for measurement.	
In-Line	Chemical analysis is done in situ, i.e. directly inside the process line, using a probe that is chemically sensitive.	
Non-invasive	Analysis based on a probe that does not physically interact with the sample.	

Table 1 shows the PAC main applications described by their principal sampling modes. See also Figure 2 on page 72.

It is important to realize that during the timeframe in which these developments in PAC were happening (1980s), Pierre Gy's 1998 book *Sampling for Analytical Purposes* had not yet been published. By then, TOS had gained recognition and use by many industry sectors in which understanding and managing sampling uncertainty resulted in huge financial savings (e.g., in mining, minerals processing, cement, pharmaceutical industry sectors).

Key to the success of TOS at any scale, especially in the analytical laboratory, and subsequently at manufacturing scales, was a comprehensive understanding of how sampling variation arising from *both* the compositional property of materials, the unit sampled (the sample mass), and the spatial distributional material heterogeneity, determines the quality of the analytical result. Gy revolutionized both theory and practice in realizing that the correct understanding of sampling variability needs to take into account all heterogeneity manifestations as well as the appropriate sampling procedure, a scope emphasized in DS-3077 (2024) and by Esbensen (2020, 2025).

2 Contrary to many current understandings, it is not possible to ascertain the representativity status of an individual extracted 'sample' by any characterization of the sample itself. With TOS, a representative sample is defined as the result of a representative sampling process. It is the sampling process only that can be designed, implemented and verified as representative; this is a key tenet of TOS (Danish Standards, 2024; Esbensen 2020; Esbensen 2025).

An important factor determining the possibility of securing a *representative* sample is also related to the lot geometry and size. Accordingly focus must also be on *lot dimensionality*. TOS classifies lots into four geometrical categories, i.e., lot dimensionalities: zero (0)-D, one (1)-D, two (2)-D and three (3)-D lots. This provides the basis for considering the geometry and the scale of material lots to be sampled, which also determines the scale of the sampling process (the sampling tools). (Danish Standards, 2024; Esbensen, 2020; Esbensen 2025; Romanach, 2015) describes the framework of the theory of Sampling (TOS) in more detail and gives many foundational references for the interested reader.

Applying TOS principles to analytical chemistry and later, process analytical chemistry, is one of the core focus areas for the International Pierre Gy Sampling Association (IPGSA): https://www.intsamp.org/

Having forged its beginning from very practical objectives (major industrial and trading sectors, (Esbensen et al., 2019; Esbensen, 2020; Esbensen 2025), but also from a fundamental need to scientifically define sample (vs. specimen), analytical aliquot, measurement, and analytical result, TOS fundamentally changed how sampling is viewed in key analytical domains (e.g., in *vibrational spectroscopy*, visible, NIR, RAMAN) because of the introduction of the critical concepts of sampling representativity[2], material heterogeneity, and lot dimensionality. Considered together, PAC and TOS provide a complete theoretical basis for controlling the effective total analytical result uncertainty by carefully considering and controlling the sampling process as responsible for delivering a defensible representative analytical aliquot to the domain of analysis. It is fair to say today that TOS is the agent responsible for a renewed focus on the fact that the aliquot is the only miniscule portion of the original lot that is actually analyzed. Since aliquots typically only make up from 1:103 to 1:109 of the original lot volume/mass, the role of a representative sampling process spanning six orders of magnitude cannot be undervalued!

The generously available TOS literature since 2000, concluding with the iconic compendium "Economic Arguments for Representative Sampling" (Esbensen, 2021) explored the many ways leading to a sampling bias and the resulting uncertainty that will arise in practice, mainly as related to PAT.

4. Process Analytical Technology (PAT)

Process sampling is differentiated from static sampling by virtue of the sample, or the sampler, is *moving*; one has to sample a *dynamic* material system (a heterogeneous material system at that). TOS states: "The movement involved is relative: either the matter streams, or flows, past the sampler/sampling equipment, or the sampler "walks up and down" along the extended dimension of the lot" (the latter obviously dependent upon competent involvement of appropriate engineering). From the point of view of TOS, both modes are considered equal in contributing to the TSE. Most importantly though: from a PAC or PAT perspective, the goal of sampling has not changed from static to dynamic sampling - minimization the of TSE before TAE.

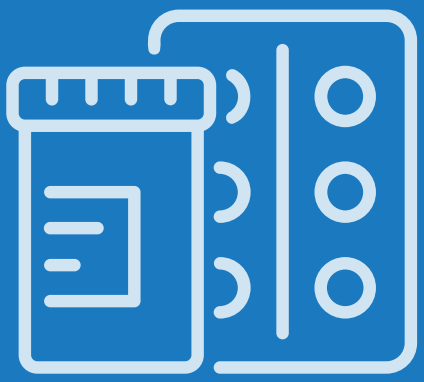
PAT, one leg of the FDA's monumental '21st century initiative for pharmaceutical quality' (see Fact box and USDA, 2004), was started in response to the FDAs concerns over low efficiency and poor quality in pharmaceutical manufacturing. The FDA devised and implemented a framework approach to encourage innovation and continuous improvement. Key achievements include new guidance documents, a quality system approach to inspections, and a shift towards process understanding and control.

The FDA stated (2004): "*The goal of PAT is to enhance understanding and control the manufacturing process, which is consistent with our current FDAs drug quality system: quality cannot be tested into products; it should be built-in or should be by design.*" This is in agreement with PAC's focus on the control of the quality of the analytical result and with the TOS control of the TSE. TOS helps achieve control over process sampling by designing valid (correct, unbiased, representative) sampling procedures (very often automated), that are qualified and continuously verified, to yield representative sensor measurement results. Figure 1 shows an archetype implementation of a PAT sensor (probe) with which to *interact* with a moving material stream. PAT sensors/probes are very nearly always multi-spectral (vibrational spectroscopy), demanding powerful *chemometric multivariate calibration and validation* (Martens & Næs, 1989; Esbensen, 2020; Esbensen, 2025). Note how all PAT sensor/probe installments must comply with TOS' demand to cover a *complete slice* of the moving material stream.

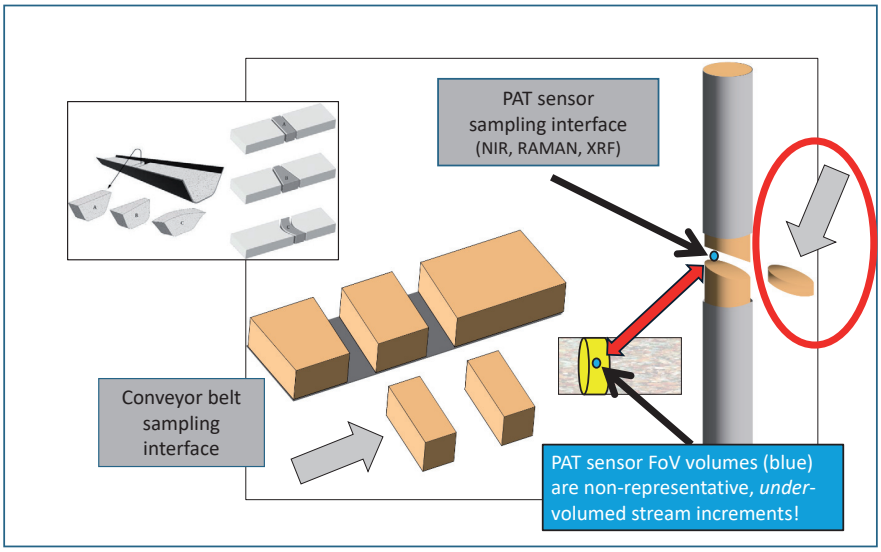
The field-of-view (FOV) of PAT sensors/probes (blue circles in Fig. 2) obviously do not cover a complete slice of the contemporary stream. This is unfortunately a massively neglected obligation in very many current 'PAT solutions', as documented in (Esbensen, 2025).

FACTBOX - 21st Century Initiative for Pharmaceutical Quality

- The FDA's initiative began in 2002 in an attempt to modernize pharmaceutical manufacturing regulation by integrating a science-based, risk-based, and quality systems approach across the product lifecycle. FDA developed a wide Quality Systems Framework and issued draft guidance for industry.
- Piloted inspection site prioritization model. Integrated risk into CMC review
- Issued PAT guidance. Promoted continuous improvement and innovation
- Collaborated with ICH, (VICH), Pharmaceutical Inspection Co-operation Scheme (PIC/S) Supported Q8, Q9, Q10 initiatives
- Updated compliance policy guide. Planned revision of 1987 guideline
- Launched pilot program. Drafted formal guidance
- Issued final guidance. Initiated rulemaking process
- Created Pharmaceutical Inspectorate. Enhanced training and certification
- Draft guidance issued. Enabled post-approval changes without prior FDA review
- Formed cross-functional team. Supported ASTM E55 standards



(CMC) - Chemistry Manufacturing and Control
(VICH) - International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products
(PIC/S) - Pharmaceutical Inspection Co-operation Scheme



Credit: KHE Consulting; used with permission.

Figure 2: Principally identical PAT sampling demands to samples extracted from conveyor belts or pipeline moving material streams.

5. PAT – Historical Development

Table 2 shows a timeline of the history of development of the FDA PAT initiative. Since its inception, PAT has seen a slow but steady growth and has had a significant impact also in many other industry sectors than pharmaceutical manufacturing. Several pivotal moments from the development of PAT have resulted in some of its successes today in 2025, as we are now entering a continuous manufacturing (CM) phase of PAT (more of which below). PAT (incorporating TOS) serves as a crucial enabler for the successful implementation and improvements in CM.

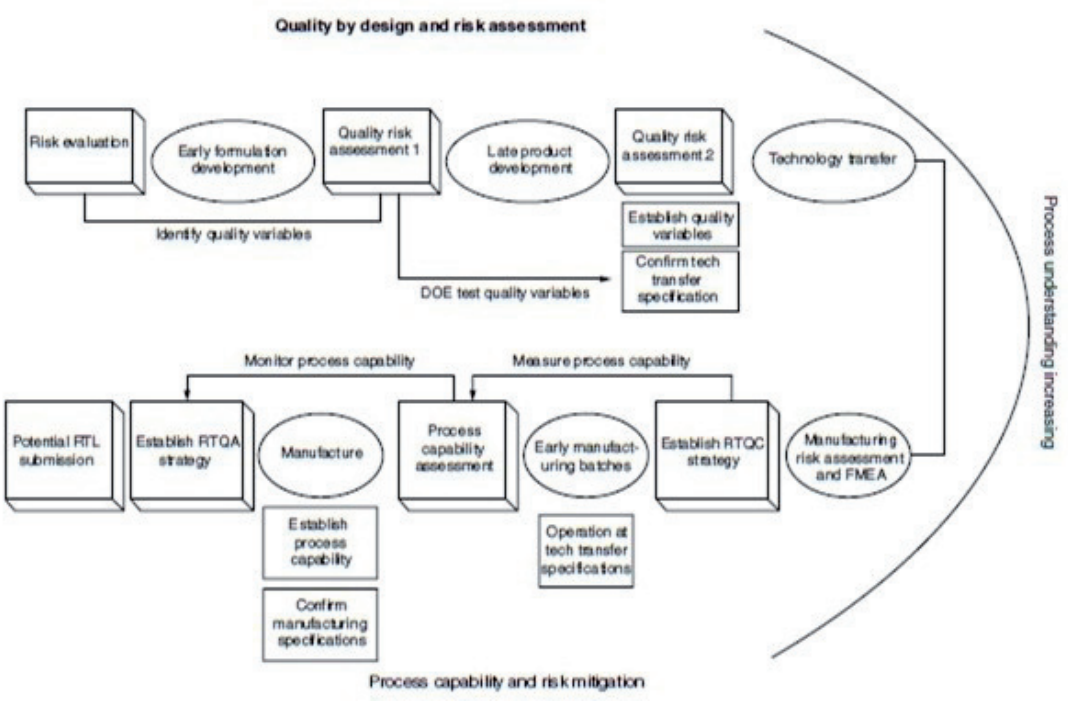
The next successful step for the development of PAT for pharmaceutical manufacturing was introducing the concept of Quality by Design (QbD).

6. Quality by Design (QbD)

Developed from the ICH, the guidance provides current thinking by the FDA on Quality by Design (QbD) as a systematic approach to pharmaceutical development. QbD emphasizes building quality into a product from the start by focusing on product and process understanding, risk management, and continuous improvement throughout the product lifecycle. This approach helps ensure product quality, enhance manufacturability, and potentially leads to greater regulatory flexibility (FDA 2009a, 2012a, 2023b). Figure 3 shows a mind map of PAT elements needed for understanding and managing process risk through designing, validating, and monitoring process variation.

Table 2: PAT Development Timeline.

1993	Early concepts of Process Analytical Technology (PAT) introduced by Tom Layoff et al. at AOAC conference.
2000	Initial proposal for PAT initiative met with limited support within FDA.
2001	**July**: Introduction of PAT topic to FDA Advisory Committee for Pharmaceutical Science. **November 16**: Key presentations at FDA Science Board set the stage for initiative: • GK Raju analyzes low efficiency in pharmaceutical manufacturing. • Doug Dean and Francis Britain highlight "don't use and don't tell" culture at Pfizer. • Ray Scherzer emphasizes cultural and historical barriers to quality by design.
2002	**January**: Establishment of PAT subcommittee with industry and academia representation. **June**: PAT initiative formally launched. Goals: improve manufacturing efficiency, reduce costs, address FDA resource challenges.
2003	September 11th and rising drug affordability concerns add urgency to initiative. Shift towards CGMPs initiative addressing broader quality systems.
2004	**July**: Finalization of PAT Guidance for Innovative Manufacturing and Product Development Quality Assurance. **September**: Major announcement with over 18 guidance documents issued (including PAT Guidance, Aseptic Manufacturing Guidance, Quality System Approach to CGMP Inspections). Start of paradigm shift within FDA: • Reduced turf issues between CMC review and CGMP inspection. • Scientific assessment prioritized over procedural compliance. • Process validation redefined with focus on understanding and control. • International collaboration through (ICH) Q8 (Risk Assessment & Risk Management), Q9 (Quality), and potential Q10 (Continuous Improvement & Change Control).
Ongoing & Future	Five major pharma companies led the way in adopting PAT principles and submitting innovative proposals. • Continuous improvement in efficiency and reduced regulatory burden expected for compliant companies. • Principles of systems approach and quality by design applied to other initiatives like Critical Path. • International collaboration and harmonization efforts continue. • The timeline focuses on early key milestones and highlights. Further details and specific dates for individual actions can be found in official FDA records and publications. The initiative is ongoing and continues to evolve into CM.



Credit: R.S. Chisholm; used with permission.

Figure 3: PAT Mind Map.

Two key practices that must be integrated with QbD elements from product development practices are risk management and an appropriate quality management system:

1. There must be a QbD-aligned *sampling plan* detailing the method, procedure, quantity, frequency, and location of sampling at various stages of the process, including raw material, in-process, and finished product analysis, according to data integrity and good documentation practices (FDA 2018). TOS is a critical success factor in this endeavor.
2. Special attention needs to be paid when sampling heterogeneous materials, where variations in composition or properties necessitate well-designed, flexible *sampling strategies* to always ensure representativeness. The statistical discipline Design of Experiment (DOE) helps understand the relationship between input variables (e.g., process settings) and output parameters (e.g., product quality). DoE is an important component of QbD. It provides meaningful data with which to validate that a process consistently produces a product meeting its specifications e.g., via Critical Quality Attribute (CQA) monitoring, which is crucial for FDA compliance (Adelberg, 2024).

7. Process Validation

Process validation is the first necessary step for the advancement of PAT in drug and product manufacturing. Process validation (Adelberg, 2024) is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validations occur in three stages:

Stage 1 – Process Design: The commercial manufacturing process is *defined* during this stage based on knowledge gained through *R&D, pilot studies and scale-up activities*.

Stage 2 – Process Qualification: During this stage, the process design is evaluated to determine if the process is capable of *reproducible commercial manufacturing*.

Stage 3 – Continued Process Verification: *Ongoing assurance (QC/QA/QM)* is to be gained during routine production that the process remains in a *state of control*.

Incorporating process sampling methods and technologies into drug and product remanufacturing processes, according to the TOS, will ensure that the variability of the sampling method, and the representativity of the resulting samples are controlled, qualified, and continuously verified.

ICH is an organization involving regulators and the pharmaceutical industry worldwide. Its purpose is to improve efficiency of new drug development and registration processes, promote public health, prevent duplication of clinical trials in humans and minimize the use of animal testing without compromising safety and effectiveness (Adelberg, 2024). The following topics introduce the ICH guidelines for drug substance manufacturing, drug product lifecycle, Continuous Manufacturing of Drug Substances and Drug Products, and analytical method development.

8. Development and Manufacture of Drug Substances

The primary sampling principles of the TOS are founded on the concept of heterogeneity, a.o., defined by the concept of lot dimensionality. This approach can be shown to be related to the core principles discussed in the development and manufacture of drug substances (FDA, 2012b), these being risk management, quality assurance and process control. Several properties of pharmaceutical starting materials may be desirable and considered in order to provide strict control over the Critical Quality Attributes (CQA) of the final drug substance - especially impurities, but also moisture, particle size, residual solvents and heavy metals for instance. However, it is indeed remarkable how much evidence can be found today in peer-reviewed publications in which TOS postulates that only one criterion is necessary to ensure that the starting materials are correctly selected and justified based on the requirements for representative sampling (Table 3).

Sampling representativity is the general criterion to be considered for materials' characterization (e.g., physical, chemical, biological, and microbiological properties) and subsequent processing (sub-sampling) must also be carried out by TOS-complying Sample Unit Operations (SUO) (Esbensen and Wagner, 2015).

Recall that sampling of materials involved in manufacturing of drug substances are typically performed by one of five PAC sampling modes (Table 1). Measurement characteristics for each mode may vary and depend on whether or not samples are taken directly from a process (and are thus 'consumed') or material properties are measured indirectly (non-invasively and non-destructively). Because of these demands proper selection and justification of drug manufacturing starting materials can be considered by design (i.e., critical process parameters (CPPs) and critical quality attributes (CQAs). This means that risk management, quality assurance and process control strategy can be properly addressed based on a sampling lifecycle strategy framework 'from starting materials to final drug substance'.

9. Bias testing – brief interlude

Within pharma there has been a longstanding focus on bias testing, as an integral part of Quality Control and Quality Assurance (QC/QA). However, in the last 5-10 years it has gradually become clear that this is a severely limited approach as concerns representativity. Bias testing does not guarantee representativity across time, material batches, or process changes. And anyway, bias testing is a *post hoc* approach that positively *invites* many batch rejections (unwanted). Much better to adopt TOS' approach of designing, implementing and verifying unbiased sampling processes (Danish Standards, 2024; Esbensen, 2020; Esbensen, 2025; Romanach, 2025).

Table 3: Trying to Ensure Representativity Through Bias Testing.

Purpose of Bias Testing	Validate that a sampling system yields representative samples compared to a reference method.
Reference Methods	Commonly used: Stopped Belt Sampling, Manual Grab Sampling, or Composite Reference Sampling.
Limitations	Bias tests reflect only the conditions during testing. They do not guarantee representativity across time, material batches, or process changes.
Correct Sampling First	Eliminate Incorrect Sampling Errors (ISE) before optimizing for precision, i.e., minimizing Correct Sampling Errors (CSE), e.g., increasing the operative number of increments.
Regulatory Implication	A fully TOS-compliant sampling plus analysis system will be able to reduce or eliminate the need for repeated bias testing, supporting long-term compliance and audit readiness.

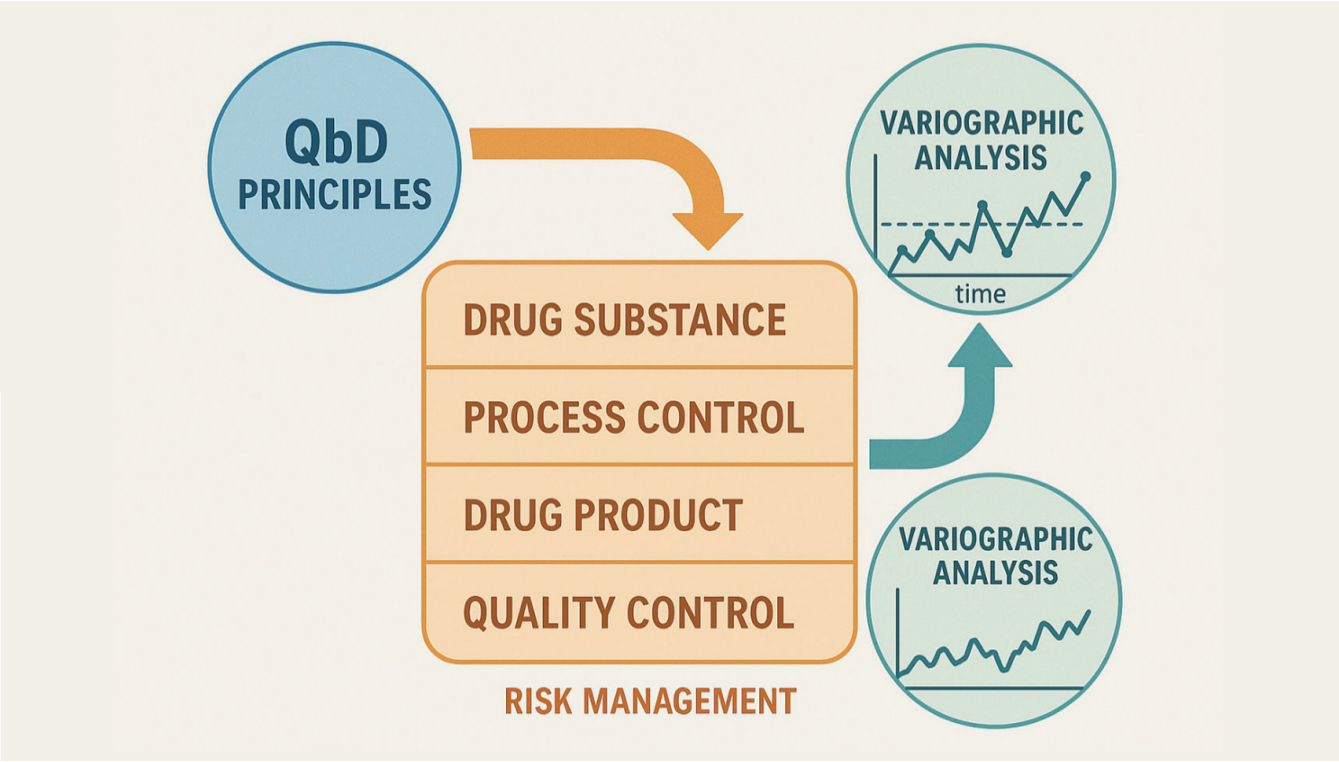
10. Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management Guidance for Industry

Following a sampling management lifecycle strategy designed to control the variability of analytical results by counteracting the adverse effects from material composition and spatial distribution heterogeneity throughout a manufacturing process (i.e., drug product and substance development, registration, and launch), this guidance addresses the commercial phase of the product lifecycle, particularly post approval changes through specially developed tools for managing and communicating control and control of changes over the process (FDA, 2021). More importantly, this strategy is one that links and harmonizes manufacturing process control regulations across three global regions: European Union (EU), United States (FDA), and Japan (MHLW/PMDA). This provides a way for the set of requirements for procedures and documentation elaborated on in the TOS standard (Danish Standards, 2024), to be easily and readily applied seamlessly to the drug substance and product manufacturing domain. For instance, sampling and measurement error management can be used for supporting the qualification of sampling hardware and software. Validation can be performed on process and sampling/measurement methods (modes). This data provides the desired knowledge to understand the CPP necessary to manage process variability resulting from sampling uncertainty.

This tool provides meaningful diagnosis as to root causes, and can be used to scientifically communicate, implement and assess changes so that the final quality of analytical results from pharmaceutical product lifecycle framework, risk management, and manufacturing processes remain in a state of control. Figure 4 shows how QbD principles guide process understanding and design space, how risk management identifies and mitigates critical quality risks, and how variographic analysis (the most recent innovation in pharma from the sampling domain (TOS), see a parallel article in this issue of SST) monitors spatial and temporal variability in drug substance and product manufacturing. Each element flows into the next, supporting a robust control strategy.

11. Continuous Manufacturing of Drug Substances and Drug Products Guidance for Industry

Movilla-Meza et al. (2025) reviewed several CM studies where QbD principles, PAT tools, and variographic analysis were assessed for improving PAT development, implementation, and quality control. They concluded and showed that it is possible to differentiate process variability from sampling and analytical errors.



Credit: Gary Richie; used with permission.

Figure 4: Sampling / Measurement Lifecycle: TOS Integrated with PAC/T Principles: A. QbD Principles B. Risk Management C. Variographic Analysis.

This becomes the central thesis and justification for designing a sampling strategy in the widest scope possible (sampling plan, validation plan, quality plan, lifecycle management, and a communication plan) for filing for approval and post approval changes to a pharmaceutical process and design space (FDA, 2023a). This guidance can use and rely on the TOS framework for adhering to a scientific, risk-based approach for addressing the sampling mode, placement, heterogeneity, dimensionality, and frequency. Movilla-Meza, et al. (2025) conclude:

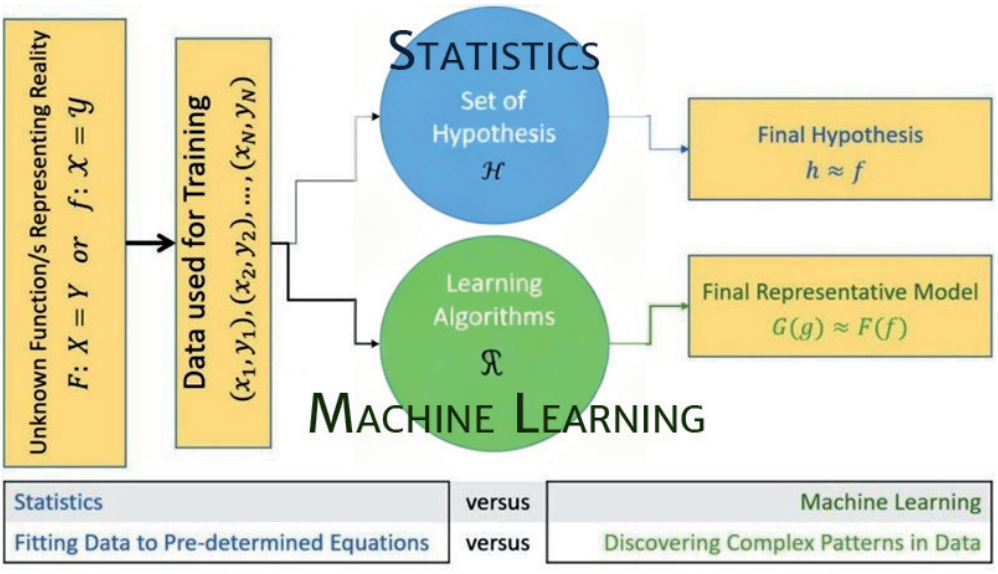
TOS has guided the sampling of CM processes. The repeatability study and variographic analysis have provided a greater understanding of the sources of error in PAT methods used in CM. Future studies are needed to better understand the cyclical behavior that is observed in variograms. PAT has progressed over the last 20 years and found a role in maintaining the state of control in CM processes.

12. Analytical Procedure Development

In the first ever published book on chemometrics by Sharif et al. (1986), the authors introduce the reader to sampling in the first chapter. A review of this chapter and its references show that the state of the art at the time this was written was rooted exclusively in classical statistical theory. While ample consideration is given to representativity of sampling from a traditional statistical population, it does not address how ill-reflected sampling for material composition will cause significant bias and other sampling error variability.

This difference between varying analytical results (statistical difference) is due to physical properties differences in the heterogeneity of materials. The physical and mathematical nature of analytical results is now superseded by Artificial Intelligence and Machine Learning, and surpassing both the statistical and physical nature of reality, by instead defining the rules leading to steps for finding a solution of a sampling reality for any given material produced by any given process (Figure 5).

From the *Journal of Petroleum Technology*, November 10, 2019, Gy's perspective is simple. A sample's heterogenous nature necessitates counteraction in the sampling process; this is the only way to obtain representativity. This solution is rooted in a thorough understanding of material composition and spatial heterogeneity - not in probability (Pierre Gy is credited with this famous statement: "Sampling—should not be gambling!". Gy powerfully showed that the practice of *grab sampling* is a very poor practice due to its guaranteed lack of representativeness, violating TOS' first governing principle (GP-1), the Fundamental Sampling Principle. This observation goes to the heart of sampling understanding at the time and illustrates the gap that existed in 1986 for sampling as a source of uncertainty also for analytical results. Gy's understanding puts to bed the false notion that sampling error originates purely from statistical properties rather than from inadequate sampling of heterogeneous materials. It would not be



Credit: Mohagheghi, 2019; used with permission.

Figure 5: Statistics versus AI and Machine Learning.

until twelve years later that Gy publishes his seminal *Sampling for Analytical Purposes* (1998), explaining how sampling theory and practice must be considered - not as a statistical matter - but from the basis of proper understanding of material properties based on the principles of physics and empirical evidence, substantiated by physical experimentation.

In today's the guidance for analytical procedure development manual (FDA, 2024), sampling is considered from the following points:

1. The measurement point(s) should be chosen so always to allow representative process sampling, and
2. The sampling interface must remain consistent over the duration of manufacturing and must be robust with regard to the expected processing and environmental variations.

Both these conditions are now aligned with TOS' control strategy for reducing TSE.

The Danish Standard (2024), *Representative Sampling — Horizontal standard* and ICH Q14 (adopted by FDA) answer different but *complementary* questions: TOS ensures that samples are demonstrably representative of the material batch, lot or process, while Q14 ensures the analytical procedure turns samples into reliable measurements across the full product lifecycle. Used together, these guiding documents close the "sampling-to-measurement" loop. These approaches are listed and compared with each other in Table 4.

Table 4: Comparison of the international 'DS 3077:2024' sampling standard with FDA's 'Guidance for Analytical Procedure Development' (Danish Standards, 2024; FDA, 2024)

Dimension	TOS Danish Standard (DS 3077)	ICH Q14 Analytical Procedure Development (FDA-adopted)
Scope	Representative sampling across materials, matrices, and processes	Development, justification, and lifecycle management of analytical procedures
Primary objective	Eliminate sampling bias and control sampling + subsampling + preparation errors to achieve representativeness	Define, justify, and control the method so results are fit for intended use via minimal or enhanced approaches
Core concept	Total Sampling Error taxonomy (correctness vs precision), heterogeneity scales, correct sampling/lot delineation, increment design, composite/pulverization, variography	Analytical Target Profile (ATP); science- and risk-based development; robustness studies; control strategy; Established Conditions (ECs); lifecycle/post-approval change pathways
Risk management	Systematic identification and removal/mitigation of sampling bias sources; design-based error control	Quality risk management per ICH Q9; knowledge- and risk-based identification of critical method parameters and ranges; enhanced approach modeling
Validation link	Focus on sampling correctness and precision; validation pertains to sampling performance and variance components	Paired with ICH Q2(R2) for validation of analytical procedures (accuracy, precision, specificity, etc.)
Deliverables	Sampling plan and SOPs; designed sampling tools and increment protocols; mixing/compositing instructions; documentation of heterogeneity and error control	ATP; development summary (minimal or enhanced); robustness and parameter ranges; method control strategy; ECs; lifecycle and change management dossier
Multivariate/advanced use	Variography, heterogeneity modeling, spatial/temporal sampling designs	Guidance includes multivariate analytical procedures and Real-Time Release Testing considerations
Regulatory status	Horizontal standard widely referenced in industries; not a drug-specific regulatory guideline	International guideline finalized Nov 1, 2023; adopted by FDA Mar 2024; complements ICH Q2(R2)

13. Summary

This chapter traced the historical, technical, and regulatory milestones that shaped PAT into a comprehensive framework for ensuring pharmaceutical product quality through real-time process understanding and control. It was shown how it is highly beneficial for society, that the modern PAT concept/framework has also been found to be applicable in many other industry sectors.

At the heart of this transformation is the recognition that sampling is not merely a preparatory step but is in fact a critical determinant of analytical reliability. The incorporation of TOS principles, particularly the concepts of material heterogeneity, lot dimensionality, Total Sampling Error (TSE) and sampling process supremacy with regard to representativity - has elevated the role of sampling from being viewed as but a procedural necessity to a scientifically governed critical discipline.

The convergence of PAC, PAT, and TOS provides a unique, powerful *unified strategy* for minimizing uncertainty, maximizing process efficiency, and ensuring regulatory compliance across the product lifecycle (pharmaceutical).

As pharmaceutical and other *similar* industries move forward, the continued refinement of sampling strategies, sensor technologies, and data analytics will grow in potential impact. The future of PAT lies not only in further technological innovation but more and more in the disciplined application of scientific principles that *bridge* the gap between [sampling-*and*-measurement] and optimal QC/QA and decision-making. This article presented a hopefully inspiring empowering scope of potential further PAT impact(s) in industry sectors already significantly relying on TOS: process sampling and PAT join forces for the future.

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Review: "Process Analytical Technology – Spectroscopic Tools and Implementation Strategies for the Chemical and Pharmaceutical Industries"

By Kim H. Esbensen[1]

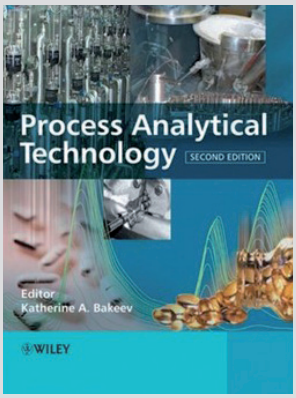
DOI: 10.62178/sst.004.003

1. A worthy companion

This 2010 Wiley textbook (2nd ed.) is rightly called "The PAT Bible" across many scientific disciplines and applied technology industry sectors, e.g., analysis, vibrational spectroscopy, NIR, RAMAN, chemometrics, process engineering, and sampling. A review of the first edition (launched in 2005) stated: "This book provides an excellent first port of call for anyone seeking material and discussions to understand the area better. It deserves to be found in every library that serves those who are active in the field of Process Analytical Technology" (Current Engineering Practice).

THE BOOK

Process Analytical Technology: Spectroscopic tools and implementation strategies for the chemical and pharmaceutical industries.
Editor, Katherine A. Bakeev. Wiley Publishing.
ISBN 978-0-470-72207-7



As the editor of SST, I recommend this book enthusiastically, with no reservations what-so-ever! If you are reading (in) this issue of SST, it is probably because its focus on PAT is of significant interest to you. As soon as you have finished reading the articles curated here, it is time to go on the internet to order this book! Why? Answering this question is the world's easiest job, as the blurb(s) for 'the PAT Bible' are extensive, very informative and scientifically impeccable - see below.

But first, allow one anecdote. Fifteen minutes after the publication of the first (2005) edition, Editor Bakeev received a very stern phone call from an irate younger version of the present SST editor: "Congratulations on a major achievement – but you have omitted the most fundamental critical success factor for PAT to be scientifically successful: representative sampling of the process segment to be analysed by one of the many, impeccably described analytical modalities in this wonderful compendium!" [I have toned down considerably this rendition of my then remarks for the sake of politeness].

All hail and praise to Ms. Bakeev, who readily agreed, with no equivocation or excuse! So, it was decided I should write up a chapter on the missing topic: Hey Presto! This is why one finds a new chapter 3 in the 2nd ed. entitled: "Process Sampling: Theory of Sampling (TOS) – the missing link in Process Analytical Technologies (PAT)".

2. Reviews of the book (both editions):

1st Edition: The use of real or near real time measurement of chemical production process parameters as the basis for achieving control or optimisation of a manufacturing process has wide application in the petrochemical, food and chemical industries. Process analytical chemistry (PAC), or process analytical technology (PAT) as it has recently been called, is now being deployed in the pharmaceutical industry, where it is seen as a technology that can help companies to improve their conformity with manufacturing compliance regulations. The objective of this book is to provide a starting point for implementing process analytical chemistry tools in process monitoring applications or as part of a total quality management system.

1 KHE Consulting, Copenhagen, Denmark

Written from the perspective of the spectroscopist required to implant PAT tools in a process environment, attention is focused on measurements that are made in process at-line or off-line, providing data on product during manufacture.

2nd Edition: Process Analytical Technology explores the concepts of PAT and its application in the chemical and pharmaceutical industry from the point of view of the analytical chemist. In this 2nd ed edition all of the original chapters have been updated and revised, and new chapters covering the important topics of sampling, NMR, fluorescence, and acoustic chemometrics have been added. Coverage includes: Implementation of Process Analytical Technologies UV-Visible Spectroscopy for On-line Analysis Infrared Spectroscopy for Process Analytical Applications Process Raman Spectroscopy Process NMR Spectrscopy: Technology and On-line Applications Fluorescent Sensing and Process Analytical Applications Chemometrics in Process Analytical Technology (PAT) On-Line PAT Applications of Spectroscopy in the Pharmaceutical Industry Future Trends for PAT for Increased Process Understanding and Growing Applications in Biomanufacturing NIR Chemical Imaging.

LIST-OF-CHAPTERS (2ND EDITION):

1. Overview of Process Analysis and PAT
2. Implementation of Process Analytical Technologies
3. Process Sampling: Theory of Sampling (TOS) – the missing link in Process Analytical Technologies
4. UV-visible Spectroscopy for On-Line Analysis
5. Near-infrared Spectroscopy for process Analytical Technology: Theory, Technology and Implementation
6. Infrared Spectroscopy for Process Analytical Applications
7. Raman Spectroscopy
8. Near-infrared Chemical Imaging for Product and Process Understanding
9. Acoustic Chemometric Monitoring of Industrial Production Processes
10. Process NMR Spectroscopy: Technology and On-line Applications
11. Fluorescent Sensing and Process Analytical Applications
12. Chemometrics in Process Analytical Technologies (PAT)
13. On-line PAT Applications of Spectroscopy in the Pharmaceutical Industry
14. NIR Spectroscopy in Pharmaceutical Analysis: Off-line and At-line PAT Applications
15. Near-infrared Spectroscopy (NIR) as a PAT tool in the Chemical Industry: Added Value and implementation Challenges
16. Future Trends for PAT for Increased Process Understanding and Growing Applications In Biomanufacturing

This volume is an important starting point for anyone wanting to implement PAT and is intended not only to assist a newcomer to the field but also to provide up-to-date information for those who practice process analytical chemistry and PAT. It is relevant for chemists, chemical and process engineers, and analytical chemists working on process development, scale-up and production in the pharmaceutical, fine and specialty chemicals industries, as well as for academic chemistry, chemical engineering, chemometrics and pharmaceutical science research groups focusing on PAT.

As professor, I have used 'the blue book' as curriculum for master level chemical – and process engineering students for two decades. It covers practically all aspects to consider when – or rather before – considering starting up an industrial PAT project (chaps. 2,15,16). The 2nd edition (aka 'the blue book') and the present SST issue are complementary in many ways:
While the blue book carries two comprehensive textbook chapters, one on sampling (chap. 3) and one on chemometrics (chap.12), its dominating value lies in presenting essentially all principal analytical modalities that can be used for PAT purposes (chaps. 4-11), with a clear focus on two industry sectors, pharma (chaps. 13,14) and chemistry (chap.15). This is of immense usefulness for everybody getting started with PAT.

The present SST issue has been 'composed' so as to complement 'the blue book' to the fullest degree possible with a curated survey of further developments since 2010, with highlights of newer meta-theoretical and practical issues, ushering in a fresh 2025 understanding of PAT. It turns out that the concept of the process sampling interface shows up as a new, key success factor of reckoning.

Be all this as it may: Get hold of 'the blue book', 'the PAT Bible'!

Innovation – From Mining to Pharmaceutical Manufacturing – The Inspiring Role of the Theory of Sampling (TOS)

By Rodolfo Romañach[1]

DOI: 10.62178/sst.004.004

ABSTRACT

TOS has guided the author in addressing multiple challenges in the sampling and analysis of the powder blends that are compressed into the tablets that many patients ingest.
Real time measurements of pharmaceutical manufacturing processes are possible through near infrared and Raman spectroscopy. These real-time measurements form part of a systematic effort called Process Analytical Technology (PAT) designed to guarantee the quality of pharmaceutical products. In PAT sampling is performed through spectroscopic methods. Sampling errors have been identified in real time PAT measurements. This report also presents a two-fold composite sampling approach developed to improve the accuracy of the real-time spectroscopic methods. Pharmaceutical processes include 1-D lot transformations just like processes in mining and other industries. Variograms can be used to evaluate the sources of sampling and analytical errors in near infrared and Raman spectroscopic methods, even though the true mass of the sample analyzed is not known. Variographic analysis is practically custom made for continuous manufacturing of pharmaceutical formulations, providing valuable information.
As part of innovation initiatives, the author has been involved in intensive customer discovery efforts for the development of new sampling technology. The Stream Sampler Kit, inspired by the Theory of Sampling, is now commercially available for pharmaceutical processes.

1. Introduction – Sampling Always Present (overt, covert)

The author thanks the Editor for the kind invitation to share with the sampling community the story of how the Theory of Sampling (TOS) has inspired research at the University of Puerto Rico – Mayagüez campus. Research at academic institutions constantly requires writing proposals and competing for funds through calls 'Request for Proposals'. In the United States, these competitions are organized by organizations such as the National Science Foundation (NSF). TOS has become a competitive advantage in these calls for proposals.

TOS has made it possible to gain a greater understanding of how heterogeneity affects the results obtained in many PAT approaches in pharmaceutical manufacturing. The author has always studied the random and systematic errors associated with analytical methods. TOS has made it possible to obtain a greater command of the sampling errors influencing analytical results (Romañach et al., 2021).
Analytical chemists seek to extract information from data produced by a specific analytical instrument or method, to optimize current methods and to design and construct more powerful instrumentation (Booksh & Kowalski, 1994). However, most importantly, this information is critically dependent on how samples and aliquots are obtained; sampling to the fore!

The Theory of Sampling (TOS) originated in the mining industry (1950-1975) and is today progressing into many other industries (Esbensen, 2016, 2018, 2020). The present author has been asked at several World Conferences on Sampling and Blending: "What mining company do you work for?" or told: "I did not know about mining in Puerto Rico".

1 Analytical and Pharmaceutical Group, University of Puerto Rico – Mayagüez Campus, Puerto Rico.

I have then explained that I have never been in a mine (Romanach & Mendez, 2019), but that I am chemistry professor focused on improving pharmaceutical manufacturing processes! Puerto Rico is only 156 km long by 55 wide but has exports exceeding $20 billion in pharmaceutical products on a yearly basis (U.S. Bureau of Labor Statistics, 2025) to over 130 countries (Invest Puerto Rico, 2019). The attendees at world sampling conferences are always pleasantly surprised to learn that my reason for participation was to learn about the Theory of Sampling (TOS), specifically for application in pharmaceutical manufacturing.

TOS has been a great inspiration for the R&D activity in our research group at the University of Puerto Rico-Mayagüez campus. The first interaction with TOS was through Pierre Gy's book 'Sampling for Analytical Purposes' (Gy, 1998). Since then, a lot of progress has been made, recently culminating in the development of a new Stream Sampler Kit designed to sample and analyze powder blends (Romanach & Mendez, 2019). This achievement has been a significant challenge, but with very rewarding results. The Stream Sampler Kit is now commercially available, and it has also served to train graduate students who contributed to its development (Nasrala-Alvarez et al., 2025) and application for new pharmaceutical products (Alvarado-Hernández et al., 2020; Rangel-Gil et al., 2023; Sierra-Vega, Martínez-Cartagena, et al., 2020; Sierra-Vega, Romañach, et al., 2020). The Stream Sampler projects have contributed to training four Ph.D. students, two M.S. in Chemical Eng., one M.S. in Chemistry, and one M.S. in Industrial Engineering student.

2. Sampling – a personal journey

Sampling has always been a part of the author's career. The author's first job involved obtaining water samples from a lake close to an oil rig in South Louisiana. The objective was to determine whether soil from the lake was moving towards an area rich in oysters. Another project with the same independent testing laboratory was to sample frozen meat imported into the United States. This job required working in very cold freezers, opening heavy boxes of meat and using a drill to obtain an entire tubular crosscut of the slab of meat. The meat removed by the drill was then analyzed for fat and protein. At that time, I wondered why someone would pay us to damage all that meat. I later learned that if our results showed that the meat had higher fat, the importer received a discount. If the results showed higher protein; thus, less fat, the meat could then be sold at a higher price (backed by the certificate of analysis from the testing laboratory).

Regardless of the results, the meat importer always made more money with the results obtained from the independent testing lab. This was my first meeting with the economic conditions surrounding and sometimes guiding analysis.

In the author's first job in pharmaceutical manufacturing, a Quality Control laboratory supervisor complained about the high volume of solvent needed for analysis of pharmaceutical powder mixtures(Romañach, 2015). These excessive solvent volumes forced the quality control laboratory to exceed the year's budget for solvents. Each sample required about 500 mL of solvent for analysis of what was the weight of 10-20 dose units. At some point, I realized that a sample preparation error could occur when a sampling thief (spear) was used to bring the powder into a small 20 ml bottle, where some of the powder could easily be lost during material transfer. The method was 'improved' with larger wide mouth bottles which facilitated the transfer of the powder mixture from the thief, and by increasing the percentage of water in the sample preparation steps. The QC laboratory budget was also favored when a legal decision required that the same size of analytical blends be reduced to the mass of 1 – 3 the dose units (Berman, 2001). However, reduction of the analytical mass resulted in many other problems associated with the use of sample thieves (Muzzio et al., 1997), a theme that has been front and central for many activities developing since.

In 1999 the present author moved from Puerto Rico's pharmaceutical manufacturing industry to Mayagüez Campus of the University of Puerto Rico. The University has a total of 11 campuses, with Mayagüez being the campus dedicated to agriculture and engineering. Mayagüez is a land grant institution that includes farms as well the actual main campus. It was founded in 1911 and now has about 11,000 students. The Department of Chemistry recently celebrated its 75th anniversary, started its MS in Chemistry program in 1959 and its Ph.D. in Applied Chemistry in 2004. The present author came to Department with the idea of using near infrared spectroscopy for the analysis of drug content in tablets. He did not know that some of the first papers on near infrared spectroscopy were published by Professor Owen H. Wheeler at this same Chemistry Department (Wheeler, 1959, 1960) before he moved to projects on natural products, organic, and nuclear chemistry. The author worked with Wheeler in the pharmaceutical industry for several years before his retirement. He was a true gentleman and scientist who knew about many different topics.

Wheeler called near infrared spectroscopy: a neglected field study, due to lack of analytical instruments suitable for observing this spectral region. Luckily in 1999, a good near infrared spectrometer was available for the author to start his research project in the analysis of tablets (Ramirez et al., 2001). However, a pivot towards the sampling and analysis of pharmaceutical powder mixtures was required to continue the progress of the research efforts.

The multiple problems related to sampling of powder mixtures in the pharmaceutical industry coincided with the author's decision to start an academic career at the University of Puerto Rico Mayagüez campus in 1999 (Berman, 2001; Boehm et al., 2003; Romañach, 2015). Experience with many sampling issues lead to a call for proposals from Puerto Rico's INDUNIV (Industry University and Research Consortium) for novel approaches to the sampling of pharmaceutical powder mixtures. The response to this call became the author's first research grant, and the research group's first publication on the sampling and analysis of pharmaceutical powder blends (Popo et al., 2002). This paper indicated that "Stream sampling takes advantage of a process that has to occur, as tablet compression requires the flow of the blend from a hopper or bin located over the compressing machine". Stream sampling was presented as an alternative to insertion of a spear or sample thief into preselected locations of the traditional pharmaceutical blender. The group's research continued to progress and in 2019 an automated stream sampling approach was patented (Romanach & Mendez, 2019). In 2020 the first research papers with the sampler were published (Alvarado-Hernández et al., 2020; Sierra-Vega, Martínez-Cartagena, et al., 2020; Sierra- Vega, Romañach, et al., 2020). In 2024, the stream sampler was licensed by the University of Puerto Rico, and since then we call it the Stream Sampling Kit (SSK). This article presents the story of the progress made by bringing TOS into pharmaceutical manufacturing.

3. Innovation – the key focus

Innovation is encouraged by funding agencies, universities, and governments. Funding agencies guide and encourage research in academia through various calls for proposals. The National Science Foundation has a Small Business Innovation Research (SBIR) program for "supporting startups and small businesses to transform scientific discovery into products and services with commercial and societal impact" (National Science Foundation, 2025a). The SBIR program provides funds for the research that startups need to develop the intellectual property required for success. Similar programs are available in other agencies of the United States government. The many current efforts to encourage innovation have contributed greatly to focusing on the development of our group's research projects.

Proposals to the SBIR programs are strengthened if the applying researchers have performed customer discovery through the U.S. National Science Foundation Innovation Corps (I-Corps™). This immersive, intensive customer discovery program facilitates the transformation of invention to impact (National Science Foundation, 2025b). The I-Corps program seeks to help discoverers and researchers transform knowledge from the laboratory into a commercial product. The achievement of this objective requires conversations with over 100 potential customers (Constable, 2014). The interviews require that researchers face unwelcome realities. The acceptance and implementation of a good idea or product is often a slow and painful process. Many companies and people are simply used to living with a problem and have no desire to overcome it. Three I-Corps™ trainings helped our group in discussing the idea of an automated stream sampler/analyzer for flowing powder blends – focused on facilitating PAT applications. In 2017, we presented a summary the experiences of the I-Corps™ program to the sampling community at the WCSB9 in Perth (Pinzon de la Rosa et al., 2017). This presentation emphasized the importance of bringing TOS to the commercial sector, an idea that was later emphasized through a wide-spanning special issue of Spectroscopy Europe in 2021 "Economic Arguments for Representative Sampling" (Esbensen (ed), 2021) with no less than 27 key academic, technology and industry leaders contributing a massive assemblage of different scopes, objectives, hard-core results, economic and societal achievements – all because of involvement of TOS. Our group chose to focus on "Sampling in Pharmaceutical Manufacturing a Critical Business Case Element"(Romañach, 2021).

With multiple calls for innovation, it is difficult for a researcher who is confident of leading an "innovative" research program to capture what is meant by innovation. A popular book on 'Design Thinking' states that innovation requires inspiration and an open mind to new ways of thinking and moving beyond current established practices (Brown, 2009). IDEO, a highly recognized global design and innovation company, sees innovation as the effort to design something better and "Build products, services, & experiences that break through" (IDEO, 2025). The Penn Center for Innovation (The University of Pennsylvania) indicates that it "helps to translate discoveries and ideas created into new products and businesses for societal benefit"(Penn Center for Innovation, 2025).

At the University of Puerto Rico – Mayagüez Campus, innovation is developed through courses that bring together engineering students from a Design Thinking course with marketing students enrolled in a Consumer Behavior course, to develop technology-based products that address current problems faced by society (Lugo et al., 2016). Therefore, innovation is not just a new idea or research project, it requires the entire path from invention to the commercial world where it must be accepted and implemented.

4. Innovation in practice – the NIR spectroscopy example

The development and advancement of near infrared spectroscopy (NIR) could be considered an example of innovation. Chemists weigh and dissolve materials to determine their chemical composition. However, manufacturing processes are often dominated by the physical properties of materials. When a sample is dissolved, valuable information on the physical properties of samples is thrown away. Near infrared spectroscopy has emerged as a powerful technique for obtaining information on the physical properties of materials as well as their chemical composition (Ciurczak et al., 2021). Many types and brands of NIR spectrometers are now commercially available from multiple vendors. The United States Pharmacopeia (USP) which sets rigorous science and the public quality standards has a general chapter on near infrared spectroscopy (United States Pharmacopeia, 2020).

There are now guidance documents on how to submit documents involving near infrared spectroscopy to regulatory agencies (European Medicines Agency, 2014; Food and Drug Administration, 2021). Near infrared spectroscopy is clearly an example of innovation that has progressed from an idea to the commercial world where it is now used in multiple industries.

Figure 1 shows a photograph of a rock brought to our lab by a local Geology professor a few years ago. This rock was part of a beloved collection that started when the geologist was four years old. It took a few minutes to convince the professor that near infrared spectroscopy was non-destructive and would not affect the rock. As we started obtaining NIR spectra, the professor mentioned that the white area in the rock was talc. The fiber optic probe of the NIR spectrometer was focused on the white area as shown in the figure. Talc has a very distinctive O-H first overtone band in its near infrared spectrum. NIR bands are usually broad, while talc provides a sharp O-H band. The right side of figure shows the spectrum of the white area from the rock and a spectrum of a commercial talc sample purchased at a local drug store. The difference between the two is likely due to the heterogeneity of the materials. However, the most important message from this figure is that the intact rock was returned to the happy professor. Most analytical chemistry methods would require removal of the white area of the rock and dissolving it for analysis.

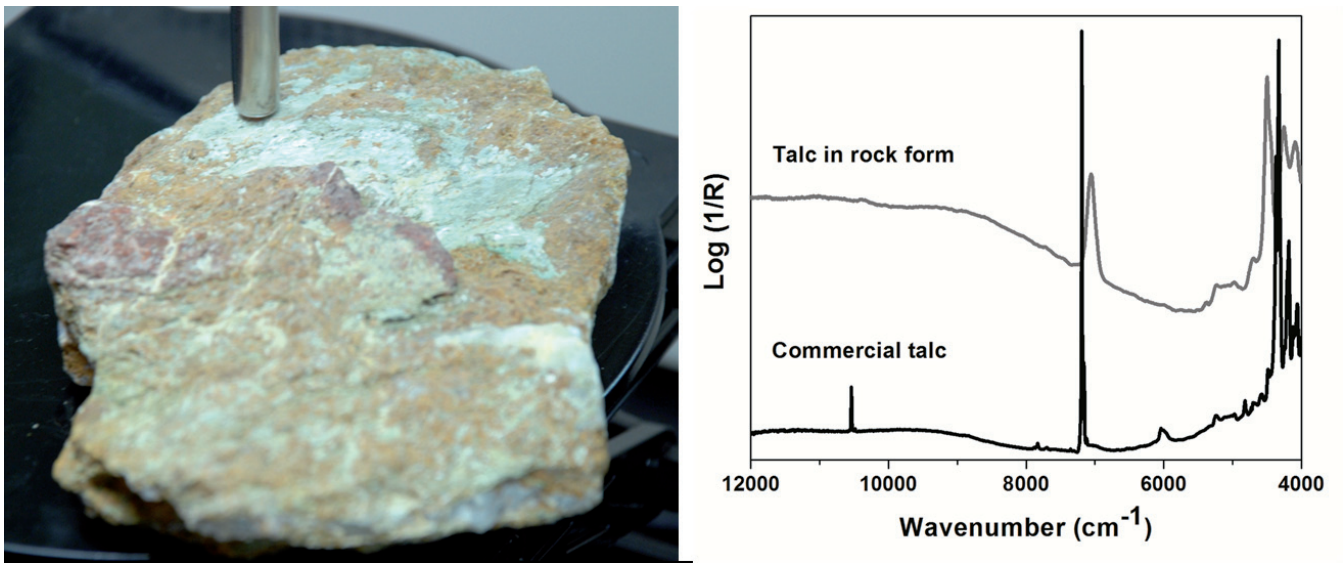


Figure 1: Left: Spectroscopic sampling of a rock from a geologist's collection through the fiber optic probe of a near infrared spectrometer. Right: spectrum of the rock (top); spectrum of a commercial talc sample (bottom).

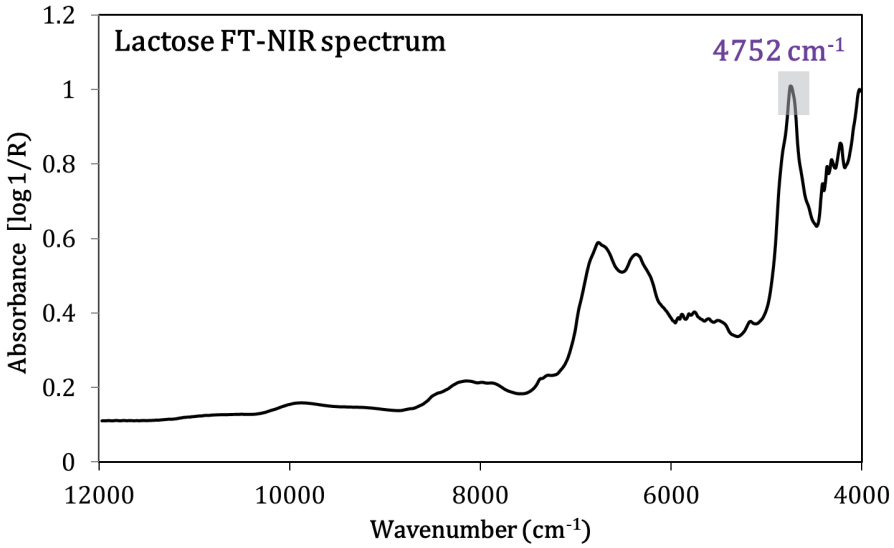


Figure 2: A NIR lactose spectrum with broad, overlapping bands.

Chemists usually wait in a laboratory and expect to receive samples when a manufacturing process is completed. However, chemists could also work with instruments installed at the manufacturing site and monitor the process as it occurs (real time). This concept was originally called Process Analytical Chemistry (Callis et al., 1987).

New ideas require time for acceptance. It was not until 2004 that Process Analytical Chemistry was adopted as a Process Analytical Technology (PAT) approach in the pharmaceutical industry (FDA, 2004). Many pharmaceutical processes involving PAT have since been approved by regulatory agencies (Vargas et al., 2018). There are now analytical instruments designed to work at/within manufacturing sites, even though in most manufacturing processes, samples are brought to the chemist who waits at the (hopefully nearby) Quality Control laboratory. Today there are many commercially available systems working with the signals from NIR PAT sensors to monitor and control pharmaceutical processes (Celikovic et al., 2025; Singh et al., 2014). The United States Pharmacopeia has recently published a general chapter on PAT for public comments to establish a comprehensive guide in alignment with scientific and regulatory standards and guidance for the implementation of PAT within pharmaceutical companies (United States Pharmacopeia, 2025). This chapter is additional evidence that PAT has walked the full path from its beginnings in the early 1980s as process analytical chemistry to its commercial adoption in pharmaceutical manufacturing.

5. Process Analytical Technologies (PAT) – the pharmaceutical case

PAT could also be considered a Human Resources initiative. Scientists have been trained to work with data and turn it into useful information. However, most pharmaceutical processes do not have information showing how the materials are transformed during the manufacturing process. A scientist may be asked to help improve the process, but most of the time the only information that is available is from when the process started, e.g., the weights of materials used, who weighed them, and when the process was completed. Because of this lack of relevant process information, it is impossible to know how the manufacturing process evolved. Scientists may provide multiple possible mechanisms for process evolution, but objective data is needed. The productivity of scientists would be increased through PAT methods which track the progress of a process.

NIR spectroscopy is now one of the most used analytical methods in PAT systems, for example offering the potential process information present in NIR spectra, which can be obtained continuously every 1 – 5 seconds without dissolving any sample material. This advantage has facilitated NIR PAT sensors to be implemented in very many pharmaceutical processes (see other contributions in this issue).

However, this same advantage also brings forth challenges. NIR spectroscopy may penetrate only up to 5 mm into the materials that are being analyzed (Iyer et al., 2002; Ortega-Zuñiga et al., 2017).

When a NIR spectrum is obtained through diffuse reflection, the radiation that returns to the detector, is only from the top 3 mm of a sensor's field-of-view (FOV) under ideal conditions (Ortega-Zuñiga et al., 2017). The radiation penetrating below 3 mm is transmitted or absorbed by the material and never returns to the detector. The depth of penetration of near infrared radiation also varies according to the properties of the material and to the frequency of the radiation. Figure 2 shows the spectrum of lactose, one of the most used excipients in pharmaceutical tablets. Lactose shows a weak broad absorbance band near 8000 cm-1. The depth of penetration of the NIR radiation is much greater at 8000 cm-1, than at the strong absorbance band around 4752 cm-1. At 4752 cm-1 the radiation is strongly absorbed by the top layers of the lactose particles. The depth of penetration is much smaller in spectral regions where the material strongly absorbs the radiation. N.B. The mass of the sample that is interacting with the NIR radiation can be estimated but is not known! NIR spectroscopists have famously been accused of being the only analysts that do not know the precise volume/mass for which an analytical result is reported(Esbensen et al., 2018; Esbensen & Romañach, 2021)! Furthermore, the material that resides closer to the surface receives more radiation than the material below (Dahm et al., 2000). Thus, NIR radiation could be interacting with only the top 1 – 2 mm of a 100 mm thick flowing blend (Romañach, 2017). In this case at least 98 mm of the flowing blend would not be sampled for analysis. In the TOS parlance, this is clearly a gross increment delimitation error (IDE), highlighting the need to improve spectral sampling for NIR methods. Clearly the geometric aspect of the process sampling interface plays a crucial role here; see another contribution to this SST issue.

Therefore, sampling is an essential element of PAT (probe sampling), even though a sample does not physically need to be removed from the process stream (Esbensen & Paasch-Mortensen, 2010). The Fundamental Sampling Principle (FSP) applies to sampling of dynamic, moving lots (process sampling) just as much as to stationary lots: all parts of the lot (or of a segment of the streaming lot) must have the same opportunity of being selected as a sample. Once this sample interacts with the analytical instrument, a spectrum or signal can often be acquired within seconds. This past year, the US Pharmacopeia published a stimuli article on 'TOS within PAT' (Romañach, 2025). The goal of stimuli articles is to seek input from the scientific community that could be used to develop future chapters in the Pharmacopeia.

6. When TOS is not the guiding principle

There is unfortunately a widespread mindset that views grab sampling as a convenient approach to quickly obtain a 'sample' and then move to what is of much more immediate interest: analysis. The challenge is to overcome this type of thinking and convince all players and stakeholders that sampling should rather always be a multi-stage sampling/sub-sampling process (Danish Standard 3077, 2024; Esbensen, 2025). Sampling is not easy and true representative sampling is challenging (Paoletti et al., 2006; Tittlemier et al., 2024), but there is no other way.

7. Continuous manufacturing

The development of continuous manufacturing processes for the manufacture of tablets is another example of innovation. Most pharmaceutical manufacturing is traditionally taking place through batch processes, where the entire batch is processed in isolated units. The materials from one unit are then moved to subsequent unit operations. In 2006, the National Science Foundation approved a proposal from Rutgers University, in partnership with Purdue University, the New Jersey Institute of Technology, and the University of Puerto Rico – Mayagüez campus to establish an Engineering Research Center on Structured Organic Particulate Systems (C-SOPS) focused on the systematic application of engineering methods to design continuous processes (Oka & Muzzio, 2022). There are now companies that provide equipment for continuous manufacturing processes and software for modeling those processes. In summary, an entire set of service providers is available for the support of continuous manufacturing. Continuous direct tablet compression has progressed from idea to the commercial world. In October 2021, continuous direct compression became the first technology to graduate from the FDA Emerging Technology program (FDA, 2025). Graduation means that submissions with continuous direct compression can be handled through the established quality assessment programs at FDA, because the reviewers now understand the technology and have the required expertise and procedures to evaluate it. Therefore, continuous manufacturing has already walked the entire path from idea to the commercial world.

Figure 3 shows the continuous manufacturing rig at the Analytical & Pharmaceutical Lab at UPR-Mayagüez where students from chemistry and chemical engineering are introduced to R&D in pharmaceutical manufacturing.

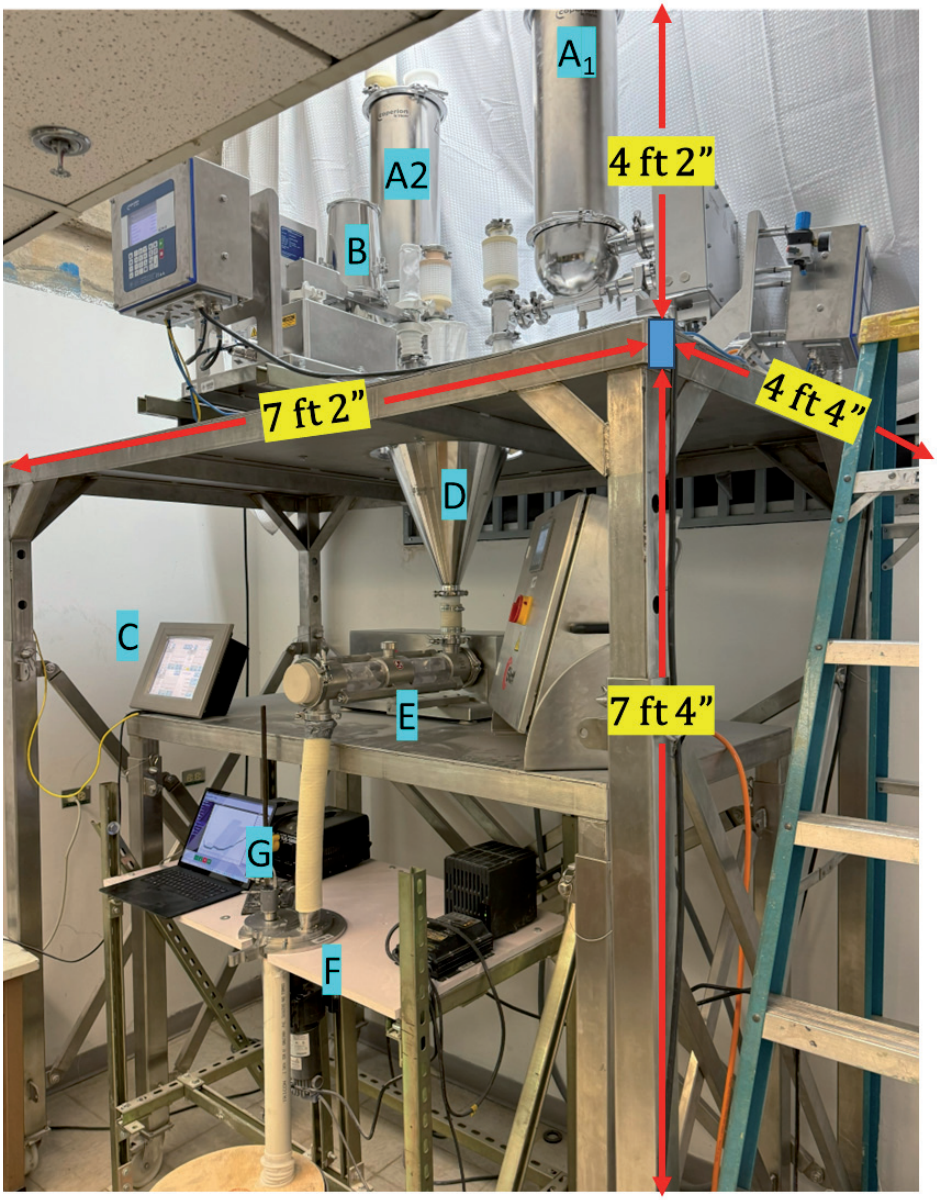


Figure 3: Experimental and pilot scale continuous manufacturing system at the University of Puerto Rico – Mayagüez dedicated to training of students and local industrial workforce. Compare this to traditional pharmaceutical manufacturing plants

The figure shows one of the advantages of continuous manufacturing - the very significant reduction in the size of the manufacturing space required. The maintenance and operation of pharmaceutical manufacturing operations is expensive so such reduction potential is highly beneficial. The design of these systems also makes it possible to use the same equipment both in research and manufacturing. In research work, the system could be run to manufacture tablets for 5 – 10 minutes (Rangel-Gil et al., 2024), while in manufacturing it could be run for 120 hours, or more, to manufacture millions of tablets (Holman et al., 2021).

With such a setup, tablets can now be made within minutes of starting an integrated continuous manufacturing system. Novel design of continuous processes is now possible through a thorough understanding of the physical properties of active pharmaceutical ingredients and excipients (Razavi et al., 2022). Therefore, transfer of continuous processes from research and development to manufacturing is now facilitated and effectuated with extreme ease. Continuous processes can be used to respond to drug shortages and make needed products easily available to patients worldwide (Lee et al., 2015; Romañach et al., 2023). Continuous manufacturing is a valuable asset to address future pandemics.

8. PAT opens up new vistas through interaction with TOS

It should be obvious why PAT is nowadays often used to monitor and control such continuous processes. Variographic analysis, as will be described below, provides valuable information of continuous processes. The potential benefit from the marriage PAT-TOS is almost unlimited.

9. Encountering TOS

The author's first encounters with TOS occurred in 2010 thanks to an invitation to write a chapter on sampling and validation of powder blends (Cullen et al., 2015). The invitation was for writing about "the general sampling approaches, sampling probes, errors and indeed sampling with NIR". The initiating literature search for this chapter revealed that many published papers and book chapters on sampling were mostly repetitive and without a progressive outlook – indeed discussing spoon sampling, coning-and-quartering and several other methods that were not practical in an industrial setting. There had to be a better approach!

The literature search revealed an application of TOS by Merck scientists (Green et al., 2005) to understand the sampling errors observed during fluid bed drying. This study was the first to introduce the concept of sampling errors to pharmaceutical applications and stated that "even the most "homogeneous", well-controlled processes are prone to sampling errors". The study included a first order approximation of sampling errors for a 300-L scale fluid bed dryer, indicating that the effect of sampling errors were reduced as moisture content became more uniform when the final moisture level was approached. The study also described efforts to reduce the sample mismatch error between spectra measured in-situ by near infrared spectroscopy and the Karl Fischer reference method which is based on extracted 'samples' and is done in the laboratory.

The second clue was from a seminal book that presented the golden rules of sampling (Allen, 2003):

- "A powder should always be sampled when in motion".
- "The whole of the stream of powder should be taken for many short increments of time in preference to part of the stream only being taken for the whole of the time".

These early Golden Rules of Sampling also indicated: "Observance of these rules, coupled with an understanding of the manner in which segregation takes place, leads to the best sampling procedure. Any method that does not follow these rules should be regarded as the second-best method, liable to lead to errors. Finally, the need for care and skill in abstracting samples cannot be over-emphasized." For connoisseurs of TOS, these are remarkable insights regarding process sampling, but here promulgated within an industry sector unknown to the TOS community.

The Allen book cited the second edition of Pierre Gy's book Sampling of Particulate Matter, Theory and Practice, published in 1982, and a 1953 article by Pierre Gy. The present author was able to obtain another book by Pierre Gy (1998), his famous "Sampling for Analytical Purposes" which marked his official start in studying the Theory of Sampling (TOS) in full earnest.

The first golden rule is addressed through "Lot Dimensionality Transformation, one of the governing principles of TOS. This golden rule is for example followed when near infrared spectra of flowing powders are obtained using the stream sampler designed in our laboratory, see further below.

The second golden rule presents another way of expressing the Fundamental Sampling Principle (FSP), which is met when a sampling process ensures that all extracted increments have an identical, non-zero extraction probability while covering the entire width and depth of the streaming material that is sampled (Danish Standard 3077, 2024). The second golden rule also seeks to avoid increment delimitation errors, when demanding that the whole of the stream (width and depth) should be sampled instead of only a part of the stream being taken for the whole of the time. Complying with this rule/principle effectively transforms a 3-D lot (e.g., on a conveyor belt, or in a pipeline) into a 1-D lot. Sampling will then only be a feature along the direction of movement (the process direction); this has a tremendous simplification potential, see the TOS literature (Esbensen, 2020).

In 2014, the author had the honor (and pleasure) of organizing the International Diffuse Reflectance conference in Chambersburg, PA. The author had a great scientific advisory group which suggested inviting the editor of SST, professor Esbensen, to the conference. The conference was organized without scheduled presentations in the afternoons providing a safe space for amenable conversations away from the stressful environments of offices and research laboratories. These fruitful conversations helped the author start to understand the intricacies of the deeper layers of Theory of Sampling. The present author is now a student and fan of 'Strategic Doing', a method for developing collaborations (Morrison, 2021).

Step 1 in Strategic Doing is to create and maintain a safe space for conversations of ideas. This safe space is essential for scientists and investors to think and develop new ideas. The different meetings and discussions with Prof. Esbensen at the World Conferences on Sampling and Blending have been very helpful in bringing together the governing principles and sampling unit operations of TOS for specific use and application within pharma.

10. The stumbling block to TOS Acceptance

The author's own stumbling block to accept TOS was that composite sampling would hide the heterogeneity of pharmaceutical blends. A quiet meeting in a brewery (before happy hour) in New Brunswick, NJ provided the safe space needed to overcome this stumbling block in a very relaxed conversation with Prof. Esbensen.

The author's concern was based on previous experience and research with pharmaceutical powder blends and reading of reports that indicated that "blending equipment is poorly characterized", and "questions and issues that are often ignored include dead spots; scale-up", and "products' tendency to segregate, agglomerate or break" (Timmermans, 2001). Therefore, there is a need to determine whether pharmaceutical blends contain poorly mixed areas which could lead to an over or underdose for a patient. How could composite sampling be implemented without the risk of hiding heterogeneity that could affect patients? This was a serious concern for the author.

The pharmaceutical blends which become tablets will always have some degree of heterogeneity at various scales between lot size and final tablet volume (Esbensen et al., 2016); therefore, it will not be homogeneous as is otherwise a much-declared goal within the traditional pharmaceutical realm. Heterogeneity will always exist as indicated by TOS (Gy, 2004), it is only a matter of to which degree, at which scale (Esbensen 2020). The issue is to evaluate the heterogeneity that is acceptable for drug products or other commercial materials.

The author finally understood that different composite sampling approaches could be evaluated through the concept of Lot Heterogeneity Characterization (one of the six Governing Principles of TOS). A composite sampling scheme can be designed to assure that a product is manufactured within its expected specifications, and composite sampling schemes could then be applied to evaluate the material produced. Composite sampling is critically needed to overcome the effect of heterogeneity (not to hide it), as otherwise the use of grab sampling (process of extracting a singular specimen), will always lead to a different, unreliable analytical result (Danish Standard 3077, 2024). Of course, composite sampling shall always comply with the Fundamental Sampling Principle. Once this stumbling block was overcome, the author continued on a much happier trajectory internalizing more and more of TOS.
Heterogeneity and Sampling Errors

Heterogeneity is in fact an unavoidable characteristic of all pharmaceutical manufacturing (at the process scale) (Romañach & Esbensen, 2015). Heterogeneity is also a feature of drug particles. The drug, often called the active pharmaceutical ingredient (API), is usually synthesized and purified at an industrial site apart from the plant that manufactures the final dose a patient receives (e.g., tablet, ointment, injectable). The API will need to be stored to be transported to the manufacturing site. Drug particles may vary in terms of particle size for which reason transport will often induce at least some form of segregation heterogeneity. Heterogeneity will occur as the API on the top of the storing container will be more exposed to moisture from the environment, while particles on the bottom of the container will be more protected from moisture. Drug particles may also exhibit polymorphism, with more than one crystal form of the drug (Reid et al., 2025). Therefore, heterogeneity is a ubiquitous feature at all scale levels including compositional variability within the final particles themselves.

Heterogeneous drug particles are usually mixed with various excipients. The tablet that a patient takes is not composed solely of drug particles. Some of the tablets have very small amounts of a potent drug and a diluent is needed to create a mass that can be compressed and then handled by the patient. Lactose and microcrystalline cellulose and two of the most common diluents, also called fillers. The blend may also include excipients to improve the flow of the particles or facilitate their disintegration. Excipients are essential in pharmaceutical manufacturing and will also show significant heterogeneity. Pharmaceutical processes further include mixing unit operations (Figure 3). Pharmaceutical unit operations such as milling and mixing are also viewed as part of the complement of five Sampling Unit Operations (SUO) in TOS (Esbensen, 2020; Danish Standard 3077, 2024). Correct representative sampling - and analysis - of pharmaceutical blends destined to become tablets have constituted the major objective for a dominating part of the research effort of our lab during the past 25 years.

11. Composite Sampling through Spectroscopy – a novel TOS perspective?

Composite sampling does not necessarily require physical extraction of materials from a manufacturing process – PAT to the fore! Composite sampling may for example be achieved though repeated real time spectroscopic measurements of a process: Radiation from a near infrared or Raman spectrometer interacts with a small superficial mass of blend being transported or processed. These spectrometers average a number of scans into a spectrum, thereby improving analytical quality by increasing the spectral signal-to-noise ratio. If the powder flows or moves over a conveyor belt while repeated scans are acquired, this is spectral composite sampling, as illustrated in Fig. 4.

Figure 4 shows a blend with 20% (w/w) of the analyte. However, the results predicted through analysis of a single increment (grab sampling) are never 20% (w/w). The central illustration shows an example where the NIR radiation finds a 50% (w/w) concentration of the analyte. However, this is not an analytical error, as it rightly represents the true concentration of the analyte within the field-of-view (FOV) increment - this is a sampling error that can be reduced through the use of composite sampling. Figure 4 also shows an extraneous particle that will not be detected by the NIR radiation. This extraneous material will be present in the final product received by a patient, but it will not be detected in the PAT quality monitoring. This example is not a case where the NIR spectrometer is failing, it is again a spectral FOV sampling error. The concept of sampling errors is still relatively new to the analytical and pharmaceutical community, where focus overwhelmingly has been on validation of analytical methods. TOS is a welcome new scope in the pharmaceutical sector.

The mass of the material characterized by spectral sampling can be estimated through the equation shown in Figure 5. However, the most important aspect is to obtain a meaningful average spectrum in the form of a composite sample.

The understanding that composite sampling is possible with spectroscopy, which is highly desirable in pharmaceutical manufacturing, first came about in 2014 (Colón et al., 2014). A calibration model correlating features in NIR spectra with drug concentration was developed for powders moving over a conveyor belt and also for a static powder mixture deposited over a tray.

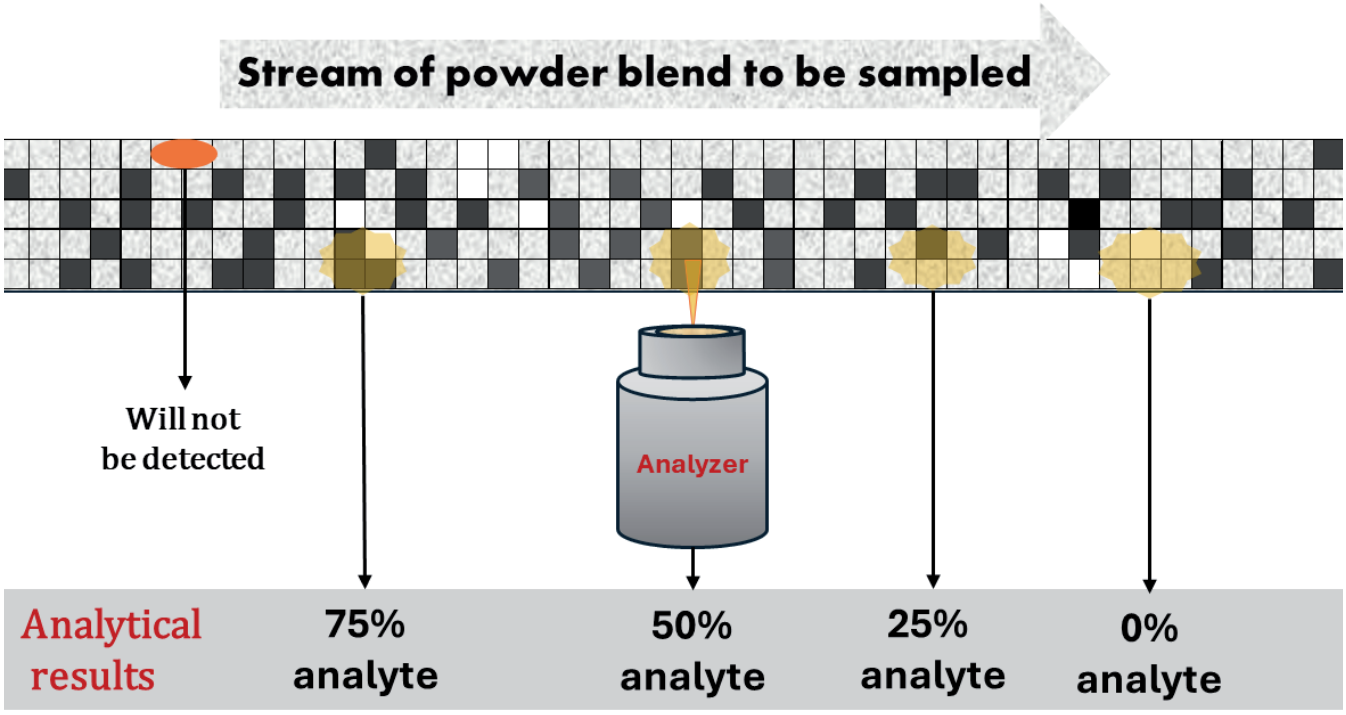


Figure 4: Principal sketch that has been helpful in describing sampling errors to chemical analysts.

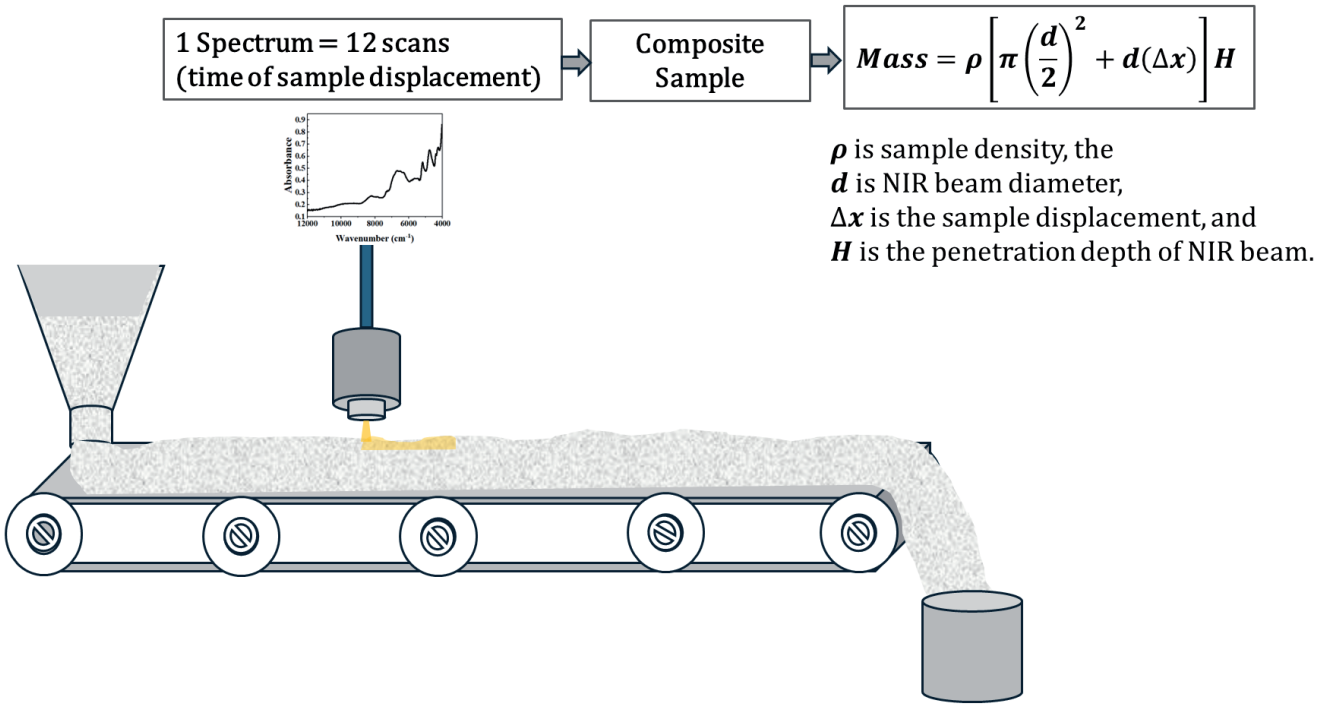


Figure 5: Sketch showing composite sampling through replicated spectroscopy of a moving target.

The results for spectra acquired while the powder was moving were three times more accurate than for the static powders deposited on a standard laboratory tray. The present author could not believe the results and spent several days trying to improve the chemometric calibration models developed by the graduate students, but without any success. The original hypothesis was that a higher signal to noise ratio would be obtained for the spectra of the static powder mixture (deposited in the tray), resulting in more accurate results. However, the 12 scans of the static powder mixture were obtained for exactly the same material and could therefore not counteract the effect from the heterogeneity of the blend.

Later systematic studies have shown that a 2-level (2-step) sample composite is possible with spectroscopic measurements. Each 'individual' spectrum obtained for a calibration model is already a composite sample in the above sense in which a certain number of scans is averaged. However, the next level of composite sampling is also achieved when multiple such spectra are obtained for each calibration blend (Esbensen et al., 2018). As an example, 16 scans may be used to obtain a spectrum of a flowing powder blend, thereby obtaining a composite sample. This could be called the first level of composite sampling.

In total 200 spectra were obtained for each blend in the calibration set. These 200 spectra represent the second level (step) in composite sampling (Rangel-Gil et al., 2024).

12. Lot Dimensionality Transformation in Pharmaceutical Manufacturing

Lot Dimensionality Transformation (LDT) occurs 'naturally' in pharmaceutical manufacturing. Raw materials, blends and/or intermediate products will flow to the unit operation where the final product is made. Pharmaceutical blends should not be sampled from pre-selected sampling locations using a sample thief, which for decades has been the paradigm within the traditional pharmaceutical realm. One cardinal reason why not, is that this approach results in particles being dragged from one location of the blender to another (Muzzio et al., 1997). There are several other disadvantages, including the fact that pharmaceutical blends are not prepared with the intent to remain in blenders. They must unavoidably flow out to compressing machines to make the tablets that patients receive. This necessary flow provides the opportunity needed (LDT) to perform the optimal sampling known to TOS: process sampling (Alvarado-Hernández et al., 2020; Sierra-Vega et al., 2019; Sierra-Vega, Romañach, et al., 2020; Rangel-Gil et al., 2024).

Lot dimensionality transformation makes it possible for all parts of the blend in an otherwise 3-D mixer to have the same opportunity of being selected as part of a sample via the moving 1-D setup. There now exist multiple published studies showing how sampling may be performed with spectroscopic methods at the feed frame of a tablet press, immediately before tablets are produced (Harms et al., 2019; Li et al., 2018, 2019; Sierra-Vega et al., 2019).
However, changes take time and unfortunately thief (spear) sampling is still used in most pharmaceutical processes (Timmermans, 2001; Pinzon de la Rosa et al., 2017).

13. Most recent development – back to mining

The pharmaceutical industry now has continuous mixing facilities (e.g., Figure 3) which are thoroughly characterized as fit-for-purpose, and which has also addressed issues related to dead-spots or scale up difficulties (Osorio et al., 2015; Osorio & Muzzio, 2016; Roth et al., 2017).

Figure 6 shows a sketch of continuous mixing equipment in the laboratory compared to lot dimensionality transformations as typical in the mining industry. The top part shows loss-in-weight gravimetric feeders.

In most processes one of these feeders will hold the drug particles. The other feeders will deliver the excipients which are required to dilute the drug particles and facilitate tablet compression. The drug and excipient particles stored in the feeders may be considered 3D lot systems. Lot dimensionality transformations occur as soon as the powder flows to the feeder as shown in Figure 6. In fact, lot dimensionality transformation occurs more than once in the continuous pharmaceutical manufacturing system. When observing crushed rocks (mineralizations, ores) moving over a conveyor belt in a mining operation (Petersen et al., 2005) have been discussed at World Conferences of Sampling Blending, this author always thinks of a continuous manufacturing pharmaceutical system – The dualities and similarities are striking!

But the lot dimensionality transformation is not unique to the mining and pharmaceutical industry - indeed all of the Governing Principles (GP) and Sampling Unit Operations (SUO) in the framework of TOS are generic and find application across a wide swath of technological and industrial sectors (Danish Standard 3077, 2024).

Once the importance of understanding 1-D transportation from the viewpoint of TOS, the following 'discovery' was inevitable.

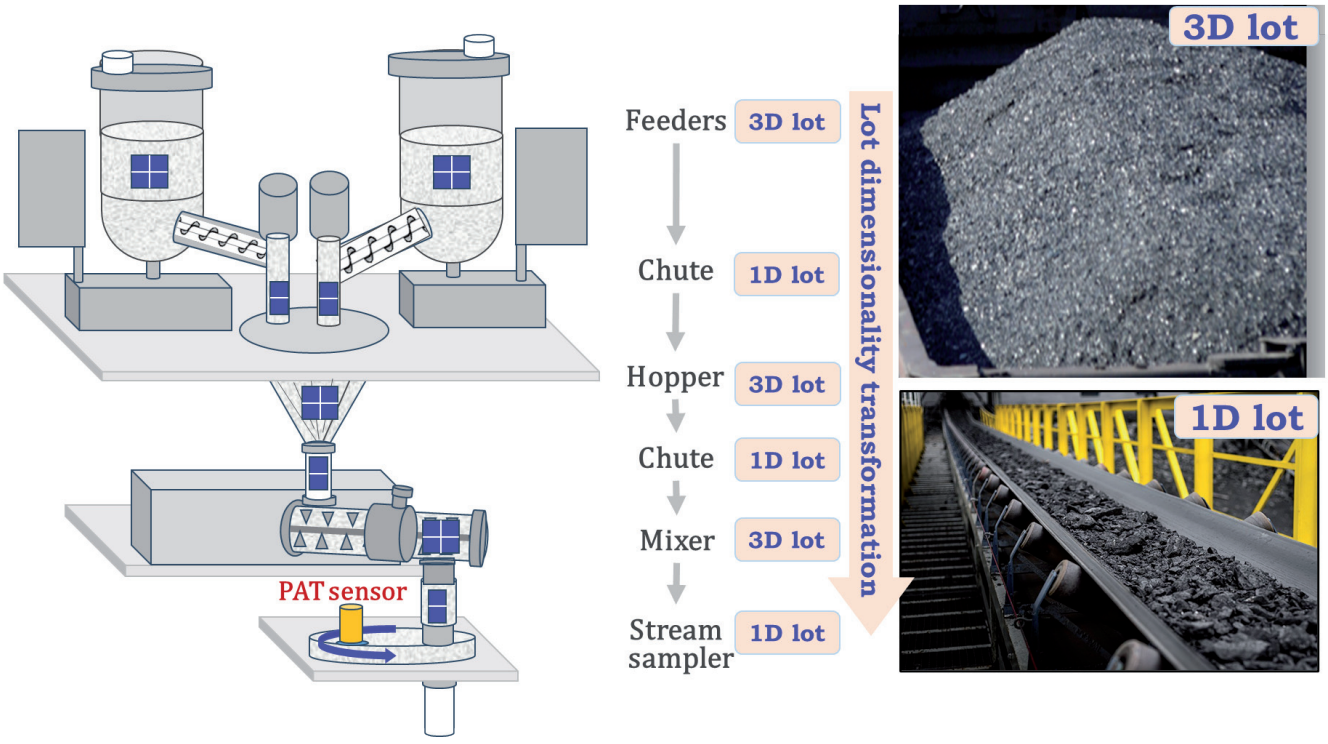


Figure 6: Parallel application of the lot dimensionality transformation principle in the pharmaceutical manufacturing system and in a mining/minerals processing operation (photos courtesy KHE Consulting Teaching Collection).

14. Variographic Analysis for Pharmaceutical Manufacturing

Variographic analysis is practically custom made for the sampling and analysis of the powder blends that flow to a compressing machine and has recently become a highly valuable asset in the evaluation of continuous manufacturing(Nasrala-Alvarez et al., 2025; Rangel-Gil et al., 2024; Romañach et al., 2018; Sánchez-Paternina et al., 2019; Vargas et al., 2018).

A variogram is based on the sequential order of samples/analytical results. NIR or Raman spectra obtained while monitoring a continuous mixing process are digitally stored and the time ordering when they are acquired is known. The variogram concept requires that a monitored process is stable. In continuous manufacturing a steady state is achieved where the input and output flows are constant over time, and the mass flux realized is constant over time (Ganesh & Reklaitis, 2020). However, in the granular reality the system is always subject to input fluctuations. Engineering systems have been developed to dampen these so that the resulting output deviations are acceptable (Singh et al., 2014).

NIR spectroscopy is now used to sample-and-analyse drug concentrations in continuous 1-D mixing processes (Movilla-Meza et al., 2025). The use of NIR spectroscopy makes it possible to determine the drug concentration every 1 – 5 seconds (depending on the spectrometer used) during the continuous mixing process, which is a landmark speeding up of pharmaceutical process monitoring. Variographics to the fore!
However, use of standard variographic analysis in PAT applications in pharma has required adapting the variogram equation slightly as the mass analyzed through near infrared or Raman spectroscopic methods can be

$$V(j) = \frac{1}{2(Q_{Total} - j)} \sum_{q=1}^{Q_{Total}-j} \left(h_{q+j} - h_q\right)^2$$

estimated but it is not known (Sánchez-Paternina et al., 2019)
where h_{q+j} and h_q are the heterogeneity contributions in each sampling location evaluated to measure the analyte, j is the lag distance (the inverse of the sampling frequency). Q_{Total} is the total number of analytical increment results acquired. V(j) represents the variance between extracted increments. The V(j) values are calculated in this study with drug concentration values predicted by chemometric NIR calibration models. The lag distance (j) is the inter-distance between pairs of API concentrations predicted by the NIR calibration model.

V(j) for a lag of 1 is calculated for the sum of squares of the differences between the first and second NIR prediction, the second and third, the third and fourth, and continues until the last two predictions. V(j) for a lag of 2 refers to the differences between the first and third NIR prediction, the second and fourth, the third and fifth, and continues until the last two predictions. There are scores of explanations of variographic analysis in the TOS literature, to which further attention is directed(Esbensen & Paasch-Mortensen, 2010; Minnitt & Esbensen, 2017; Sánchez-Paternina et al., 2019).

Figure 7 shows a variogram from a recent continuous pharmaceutical manufacturing run. Variograms are always presented together with standard control charts of the results from real time predictions obtained through a NIR or Raman spectroscopic method. Thus, the left side of the Figure 7 shows the results for a blend prepared with 50% (w/w) of the drug. The left side provides a blending profile that is considered adequate for this formulation, as all drug concentration results within 5% (w/w) of the target concentration (50% w/w). However, the variogram provides a complementary profile characterizing the blending process in more comprehensive detail. The variogram obtained is an increasing variogram where the difference between the increments is increasing as the process progresses. The variogram indicates that the mixing process has a large range, the inter-sample distance at which the mixing product becomes stable; this information is of key importance in monitoring and optimizing the specific mixing process.

Variographic analysis has shown its value in detecting subtle variations that are not so easily perceptible in the blending profiles (Nasrala-Alvarez et al., 2025; Vargas et al., 2018).

15. The Stream Sampler

The drug content of the tablets that a patient takes depends on two factors. The first is the tablet weight, which must be controlled when the tablet is compressed. The second factor is the uniformity of the blend that is compressed as a tablet. If the drug is not distributed uniformly in the blend the patient could receive a higher or lower dose of the medication.

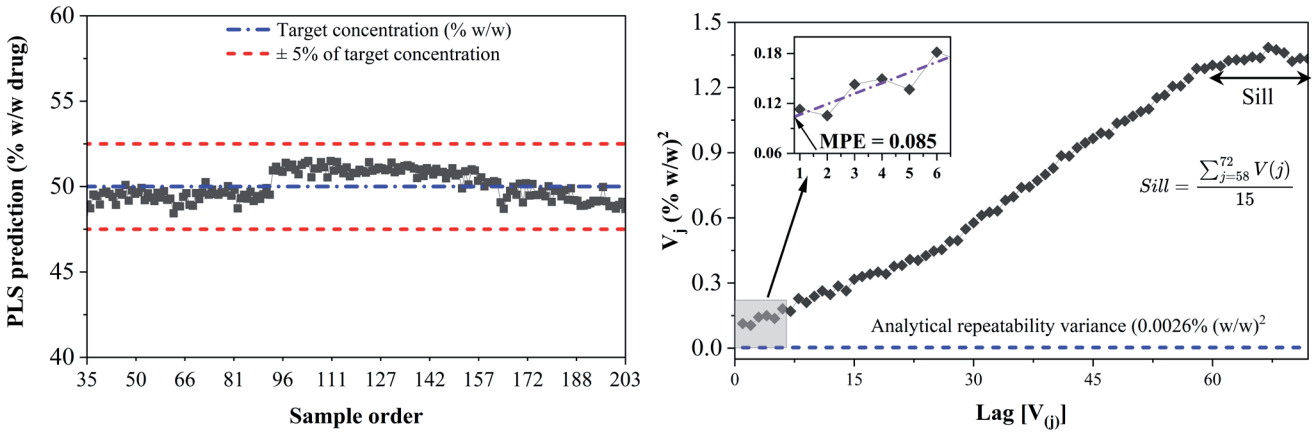


Figure 7: Left: Standard control chart of drug concentration results obtained during continuous mixing (steady state). Right: Increasing variogram characterizing the mixing process in more detail.

Sampling and analysis of the powder blends that will be compressed as tablets is required by the current Good Manufacturing Practices to assure uniformity of the drug (National Archives, 2025). The sampling and analysis of the powder blends that become tablets has been the major thrust of our research lab for the past 25 years.

This research has resulted in a patented sampler for powder blends (Nasrala Alvarez et al., 2024; Romanach & Mendez, 2019). The sampler is now commercialized as the Stream Sampler Kit (SSK) and has one paddle wheel that moves counterclockwise at 9 - 18 RPM to move the blend. The wheel has 20 paddles or blades forming twenty sectorial gaps that are filled with the powder blend. The flowing powder is confined within the paddles. The studies performed so far have shown that the physical properties of the blend are not affected by the flow through the sampler (Nasrala Alvarez et al., 2024). Figure 8 shows photographs of the current Stream Sampler Kit interfaced to three different spectrometers. The design of the sampler makes it possible to obtain a very steady powder flow even at 30 kg per hour.

The sampler is designed to avoid recirculation of the powder blend. Near infrared or Raman spectra are obtained at 180 degrees from the entrance of the powder to the sampler as shown in Figures #and #. The powder exits the stream sampler at 270 degrees from its entrance. As a result of the design, the powder blend is always entering and exiting the sampler, avoiding recirculation of any part of the powder mixture.

The sampler permits a large number of measurements of the blend uniformity through a NIR or a Raman spectrometer. These spectrometers are capable of providing spectra every 1 – 5 seconds depending on their design. The drug concentration can then be determined using multivariate calibration models (partial least squares regression a.o.). Figure 8 shows the stream sampler connected to three different spectrometers in the lab, and to the continuous mixer (MODCOS Dry Mixer 70, Glatt®, Germany).

The sampler was designed taking into consideration the principles of TOS. All parts of the batch or lot have the same opportunity of flowing into the sampler and interacting with the NIR radiation. The radiation from the spectrometers is not able to interact with the entire cross section of the flowing blend, but the sampler has been designed to minimize the thickness of the powder flow.

The development of the stream sampler has been pursued while developing a new generation of pharmaceutical scientists capable of moving PAT and TOS into commercial pharmaceutical manufacturing. The professors have not abandoned the University to pursue the development of the stream sampler. Instead, the stream sampler is currently training students from both chemistry and chemical engineering programs as shown in Figure 9, and in collaboration with a local engineering company.

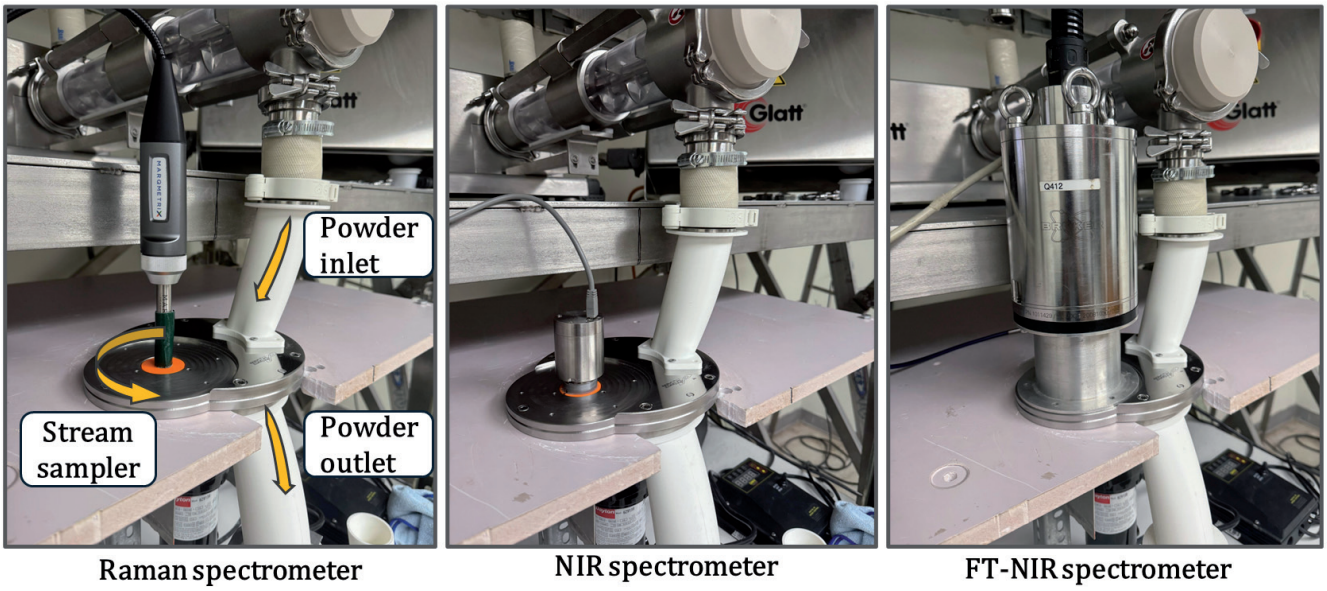


Figure 8: Stream sampler connected to three different spectrometers capable of providing real time spectra for flowing powder mixtures. Left) Marqmetrix (now Thermo) Raman spectrometer, middle) Viavi MicroNIR, and right Bruker Matrix Fourier Transform near infrared spectrometer.

Figure 9: Graduate student Dhavalkumar Patel explaining the system. Left to right: graduate student Maraliz Rivera Santiago (Chemical Engineering), and undergraduate students:Edwin Tañon Flores (Chemistry), Daianne L. Negrón Martínez (Chemical Engineering) Carlos Feliciano López, (Chemistry) and Diego Rodriguez Perez (Chemical Engineering).

16. Quality and Sampling in the Pharmaceutical Industry

The recent Covid pandemic crisis (2020–2022) showed the extreme importance of pharmaceutical manufacturing and of having a pharmaceutical industry able to respond to a global, regional or local health crisis. The right pharmaceutical products need to be accessible to patients the world over.

Since 2001, leading regulatory agencies have emphasized the need to guarantee the quality of pharmaceutical products through the QbD concept (quality by design) instead of quality by testing (European Medicines Agency, 2017). One of the tenets of this initiative is that science and regulatory agencies must protect patients (Woodcock, 2014). Even the most knowledgeable pharmaceutical scientist cannot evaluate the quality of a pharmaceutical product when lying in the intensive care unit: Scientific understanding and regulatory agencies are needed.

Quality by Design also requires sampling by design. Representativity depends on the sampling process. Representative samples only occur as a result of a representative sampling process (Danish Standard 3077, 2024).

17. Process Analytical Technology system solution in pharma

The developments described in this article were selected to showcase key examples of PAT solutions while also taking care of the specific analytical and IDE/IEE issues facing pharmaceutical systems. The still remaining issue is the partial thickness coverage (IDE/IEE) of the stream flow. However, there are still other TOS principles and ideas that need to be considered in pharmaceutical manufacturing. Additional research is needed.

18. Future goals

The next big goal is to include TOS in analytical chemistry books. It is very difficult for an analytical chemist whose entire training has been in wet chemistry and instrumental analytical methods to comprehend and visualize a sampling error. Chemists often believe that method validations already cover sampling errors. TOS needs to be incorporated into analytical chemistry textbooks to foster curiosity towards sampling errors early in the career of young chemists. These textbook chapters are the next big challenge.

The recent Euroanalysis2025 conference in Barcelona provided the opportunity to deliver three lectures on TOS: Claudia Paoletti presented on "The new frontiers in food and feed risk assessment", Kim Esbensen on: "Why analysis needs the Theory of Sampling (TOS) – the importance of the 'before analysis' domain", and the present author on "Innovation & Collaboration for Process Analytical Technology & Advanced Pharmaceutical Manufacturing". The audience's response to these presentations was encouragingly positive. The audience recognized that sampling is essential and that the concepts and ideas discussed in the three presentations need to be included more in analytical chemistry. A textbook chapter would certainly help develop TOS within the analytical community and spark genuine scientific curiosity.

The challenges and rewards of representative sampling need to be highlighted. Sampling has to be shown to be scientifically, technologically and economically attractive in spite of all the hard work needed. TOS cannot afford to be viewed as but a set of mandated high-level rules that must be followed, or a as a set of articles on the theme "I told you so, you should have followed TOS". The web site of the International Pierre Gy Sampling Association (IPGSA) and the new journal Sampling Science and Technology (SST) will certainly contribute to meeting this challenge. The reader is invited to join in this endeavor.

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This article is possible thanks to the efforts of over 30 graduate students who have contributed to the research since 1999. The collaboration with Dr. Rafael Méndez of the UPRM Chemical Engineering department has been essential for this study. As a result of this support, we now have a research lab dedicated to the training of both chemistry and chemical engineering students, and a commercial Stream Sampling Kit for use in the pharmaceutical industry The article is dedicated to the first students work on sampling together with the present author on this journey: Manuel Popo Amú, Angel Martínez Hernández, and Saly Romero-Torres. Manuel, the one of the author's first graduate students, was a devoted family man who recently passed away in his native Colombia. Angel Martínez Hernández obtained his M.S. in Chemistry in our group and is successfully leading the manufacture of pharmaceutical products. Saly Romero-Torres, a devoted mother and community leader, was the first undergraduate student to select our group and is currently a chemometrics and data science expert who leads her own consulting company.

Dhavalkumar Patel is thanked for the wonderful work with the figures.

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The Fundamental Sampling Principle (FSP) for PAT

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ABSTRACT

The critical success factor in Process Analytical Technology solutions, whether this is in the form of analysis of an extracted process sample brought to the laboratory, or in the form of a calibrated sensor analytical prediction characterising an in-situ stream segment, is the performance of the process sampling interface. The role of the interface is closely related to the Fundamental Sampling Principle (Theory of Sampling, TOS) regarding both stationary as well as moving lots. This article argues that the functionality of the process sampling interface determines whether Process Analytical Technology solutions can be implemented to furnish analytical fit-for-purpose representativity, or not. Non-compliance with a simple geometrical requirement results in biased analytical determination with unavoidable reduction in representativity. This criterium determines the fate of Process Analytical Technology solutions and their engineering implementations for most vibrational spectroscopic modalities. Thus, a single TOS-informed inspection of a process sampling interface is able to render a principal qualifying/disqualifying assessment regarding representativity – but there are important exceptions in the radio wave and gamma ray parts of the electromagnetic spectrum. This is all about the inherent heterogeneity of the material subjected to PAT sensor technology. This article presents TOS' Fundamental Sampling Principle for the Process Analytical Technology realm. There is still a way to go for further process sampling interface development.

1. Introduction

The Theory of Sampling (TOS) distinguishes between two types of lots, stationary vs. moving lots; sampling from the latter is also known as process sampling. Process sampling is a core element in Process Analytical Technologies (PAT): samples are either extracted and brought to the laboratory for analysis, or – the ultimate PAT goal – an analytical sensor facilitates 'spectral characterisation' of a material process sample without bringing anything to the laboratory.

This article presents the apparent duality between a physical sampling process and a PAT spectral sampling-and-analysis equivalent 'spectral sampling', Fig. 1, intended to help appreciating the key role of the process sampling interface (PSI) to be more fully explained. The key understanding is that both the 'dual' sampling approaches (physical vs. spectral) are subject to – and can be characterised by the same TOS sampling errors.

2. Physical sampling

In the TOS realm, process sampling is traditionally thought of as how to extract a physical sample from a moving stream of matter (a process lot), aimed at subsequently to be characterised (analysed) in the laboratory [1-4]. For the present purpose there is no need to focus on the subsequent sub-sampling steps/operations involved in getting to the final analytical aliquot as these steps are governed by the exact same TOS principles as the primary sampling step, only scaled down, size-wise [5,6].

3. Fundamental Sampling Principle (FSP) for stationary lots

The FSP stipulates that all potential increments of any lot shall have an equal probability for being physically extracted and aggregated to form a composite sample under the condition that the extracted Q increments must cover the entire lot volume with a uniform density.

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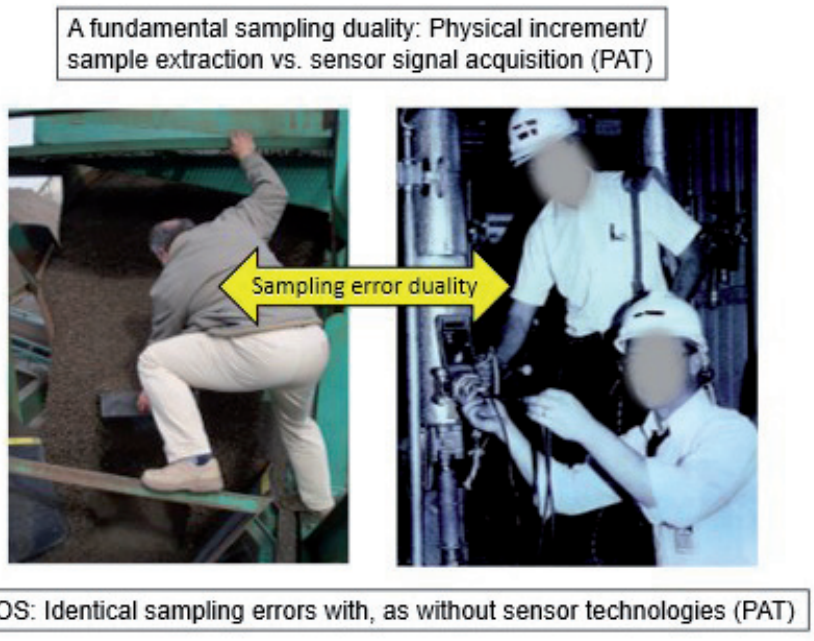


Figure 1: The apparent duality of physical sampling from –, and spectral characterisation of a process stream. With TOS' discriminating point-of-view, 'sampling' may be correct and representative or it may be imperfect, biased and therefore not representative. In Fig. 1 both illustrated sampling operations are non-representative (complementary representative sampling modes are shown in Fig. 3). *Caveat: examples are meant for illustration of principles only; no identification of company, personnel or equipment brand is intended).*

It is not only the number of increments that define the quality of the composite sample, but equally their mandated geometrical coverage. Both these attributes need to be optimised in order for the resulting composite sample to be representative of the whole lot.

Note: The representativity status of an individual sample cannot be ascertained if removed from the context of its sampling-and-analysis pathway. It is not possible to discern the representativity status of any sample in isolation. The attribute 'representative' can only be accorded to a sampling process if/when in compliance with all demands specified by TOS.

Fig. 2 shows a generic stationary lot (a schematic upper half-sphere is a stand-in for a general stockpile), showing the number of increments (Q) to be extracted to form a composite sample; for details on how to determine the optimal Q, see [2,3,5]. The sample to be extracted from an original lot is called the primary sample, which can be either a grab sample (a 'specimen' in TOS' language) or a composite sample (always to be preferred). TOS describes how grab sampling cannot be representative under any condition, for which reason only composite sampling is allowed [7,8].

Fig. 2 is a graphical rendition of the Fundamental Sampling Principle (FSP) for stationary lots, which is compared with its process lot equivalent below.

4. PAT sampling / Sensor analysis

If the primary sampling step were to be effectuated in the PAT realm, process sampling would be in the form of acquisition of a spectral characterisation of a segment of the moving stream of matter. The support for this spectral characterisation could be an extracted physical increment (a segment extracted from the moving stream) or it could be an in-situ segment of the moving flux (in-situ process increment). In the latter case, the desired PAT situation, the role of a process sampling interface comes to the fore.

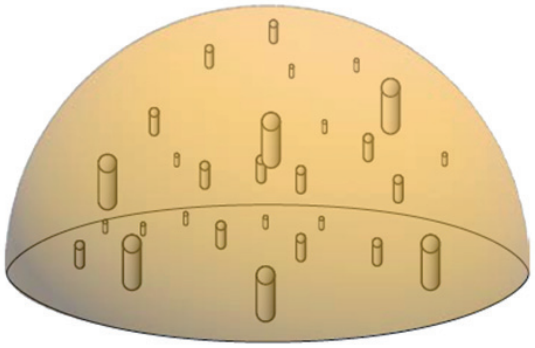
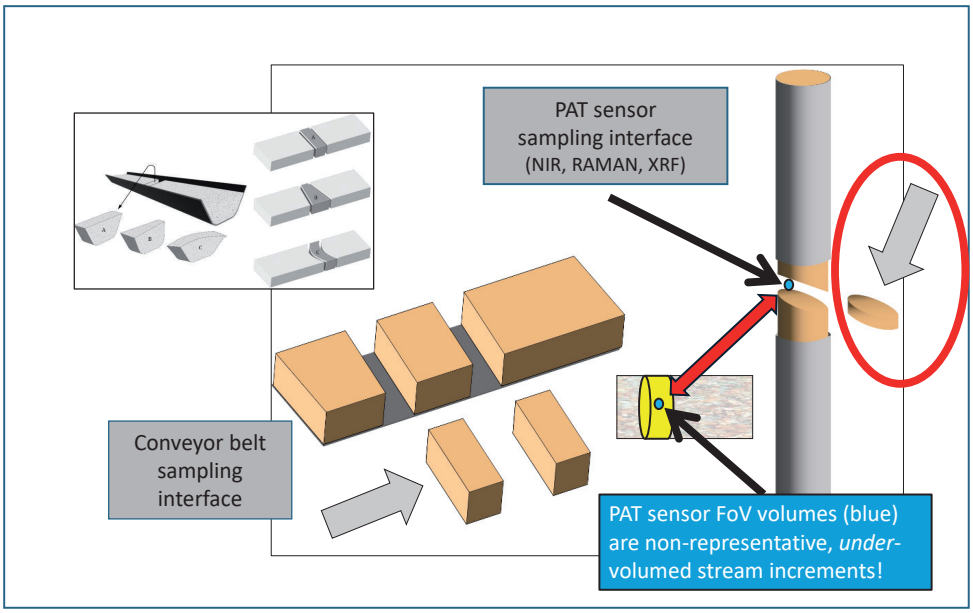


Figure 2: Graphical rendition of the Fundamental Sampling Principle (FSP) for a stationary lot. The Q increments to be extracted must cover the full lot volume with a uniform spatial density.



Credit: KHE Consulting Education Collection; used with permission.

Figure 3: Graphical rendition of the Fundamental Sampling Principle (FSP) in the PAT realm, governing the role of the process sampling interface as either delineating i) transverse conveyor belt increments, or ii) facilitating equivalent cross-section increment cuts from ducted flow through a pipeline, the geometry of which is colloquially termed an 'ice-hockey puck'.

Below is demonstrated the critical importance of proper stream segment delineation for 1-D moving lots, either of the conveyor belt – or the pipeline type, Fig. 3.

The primary role of the process sampling interface is to delineate either a transverse conveyor belt increment, or to facilitate delineation of the equivalent cross-section cut from ducted flow f.ex., through a pipeline; this latter volume is colloquially known as an ice-hockey puck. It is convenient to imagine this puck volume moving along with the ducted stream. Note how the ideal orthogonal transverse increment traces (the 'stopped belt increment configuration') across the stream become oblique because the increment cutting is taking place when the process stream is moving. This has no effect on the quality of cross-stream cuts; fully realised oblique cuts are equally good representatives of a complete slice of a flowing stream.

The TOS literature is abundant with serious warnings that the practical way many cross-belt samplers are designed and implemented are in fact biased and cannot deliver representative increments [2,3,5]. Fig. 4 is an anonymised illustration of a so-called hammer sampler - unfortunately popular in many practical installations in the mining and minerals processing industry, likely because of aggressively marketed low costs. But cost is not a driver for representativity!

The hammer sampler is an example of a Process Sampling Interface (PSI) for material streams conducted on conveyor belts, or on gravity driven or vibrating slides a.o. Fig. 4 serves to illustrate the important point that although the concept of a correct process increment may appear simple (like in the left part of Fig. 3), practical designs and implementations are not necessarily successful without OEMs being fully competent with respect to TOS. The underlying demand is of being able to extract a cut in the form of a full slice of the streaming matter (explained in full detail below). The issue here is about due diligence regarding the non-negotiable need to eliminate the two Incorrect Sampling Errors IDE and IEE during increment cutting - which is not the case for cross-belt samplers, while fully complied with for cross-stream samplers. For the present purpose it suffices to note that the physical realisation of increments can be lacking regarding representativity even for the apparently simple case of 1-D lots moved by conveyer belts: unmitigated Incorrect Sampling Errors may easily generate a biased sampling procedure, assuredly non-representative, see [2,3,5,7,8] for full introduction to TOS' arguments.

The similar situation regarding a material lot experiencing ducted flow, e.g., through a pipeline can be used to present the increment geometry needed to comply with the full cross-section demand, materialising a full slice.

Figure 4: Anonymised illustration of a particularly popular type of cross-belt sampler, the hammer sampler. For very many designs, brands and implementation this type of equipment cannot deliver a representative cross-belt cut, as extensively described, documented and warned against in the TOS literature [2,3,5]. *Caveat: this example is meant for illustration of principles only; no identification of company, personnel or equipment brand is intended.*

For a PAT solution designed to extract a representative physical sample from a pipeline flow, the full slice increment demand translates into the form of a warped ice-hockey puck, Fig. 3 (righthand side). At present there are no OEM PAT solutions in compliance with this demand; there does not exist a physical equivalent to the archetype cross-stream cutter able to cut and extract a correct warped puck slice from a pipeline flow! But contending alternatives have been put forward trying to obtain a closely similar solution, e.g., by using a bypass loop. Alas ...

However, the vast majority of PAT solutions being offered today are designed around using an analytical sensor, a probe, either to be inserted into a pipeline ducting the 1-D lot, Fig. 1., or this solution is realised by way of a Process Sampling Interface (PSI), Fig. 5.

One of the much-lauded advantages of the 'PAT revolution' is that application of sensor technology eliminates the need for sampling, i.e. eliminates the need for extraction of a laboratory sample. While the latter is true, the first is very much not [9,10-12] – to be explained below.

Figure 5: Examples of process sampling interfaces (PSI) designed to be installed as part of ducted flow. Note how flanges allow flush implementation in pipelines, while offering openings and fixtures allowing to project sensor radiation orthogonally across the material flow a.o. *Caveat: these examples are meant for illustration of principles only; no identification of company or equipment brand is intended.*

5. The PAT realm

In the PAT realm, the role of the process sampling interface (PSI) is dual:

1. Correct delineation of representative process segments to be analysed
2. Facilitating analytical interaction of a beam of sensor radiation with the material support volume realised by the sensor FoV

The potential mismatch between delineated vs. realized analytical volume is the key topic of this article.

Here is the crucial issue:
Is the PAT sensor radiation beam able to interact analytically with the full support volume (puck volume) delineated by a specific PSI? If yes, the PAT system is unbiased (sampling wise) – if no, the PAT system is biased (to an unknown degree), because being fraught with unmitigated IDE/IEE deficiencies; full background argumentation in [9,10-12].

5.1 Terminology overview

In order to avoid unnecessary confusion, a distinction must be made between no less than three types of sampling:

1. Physical sampling, which could be called sampling$_{TOS}$
2. PAT sensor sampling, which shall be called sampling$_{PAT}$
3. Statistical sampling, which could be called sampling$_{STAT}$

The many different usages and meanings of the term 'sampling' is a historical result of independent development in diverse scientific disciplines; the reader is referred to [13] for in-dept discussion. Here we only need to focus on the relationship between the first two variants: sampling$_{TOS}$ vs. sampling$_{PAT}$.

5.1.1 The many meanings of the term 'sample'

TOS stipulates that the term 'sample' shall only to be used in the meaning of a representative sample. This ties in exactly with TOS' other liberating imperative, that only a sampling process can be assigned the attribute representative – Ergo: a representative sample cannot be defined by any inherent attribute but is to be defined solely as the product of representative sampling processes. This goes for both stationary and moving, dynamic process lots – and in the laboratory as well, where samples are usually affixed with the prefix "sub" (sub-sample).

All types of extracted material portions that cannot be shown to be the result of a representative sampling process shall, in the name of clarity, henceforth be termed 'specimens'. Sub-samples derived by a non-representative mass-reduction process in the laboratory may well also have to be termed sub-specimens ...

For the present purpose, there is one last specification of importance in order to appreciate the current topic: "There are sample cells - and there are sampling cells" (the latter in the form of a sampling interface (PSI). To highlight this crucial distinction, please compare Figures 5 and 6.

Figure 6: Illustrations of a number of sample cells; compare with Fig. 5. Caveat: these examples are meant for illustration of principles only; no identification of company or equipment brand is intended.

There is empowering clarification in acknowledging the distinction between a sample cell, into which is placed an already sampled aliquot, and a sampling cell (a sampling interface) the task of which is *both* to delineate the increment to be analysed and to facilitate sensor beam interaction with precisely this material volume flowing through the interface [7,8].

Sensor radiation travelling through the PSI, as well as absorbed and reflected signal impulses, define an 'analytical pathway' through the geometrically delineated increment volume. For the present purpose it is useful to imagine this pathway in the form of a (roughly cylindrical) radiation beam penetrating from one side to the other of the increment boundaries, extending across a full cross-section distance. Contrarily, the penetration depth of reflection spectroscopic modalities (diffusion reflection, specular reflection) will only extend along a fraction of this distance, effectively interacting with only a reduced volume element in front of the sensor head, see Fig. 3 (blue circles).

As exemplification, the following argumentation focuses on NIR spectroscopy: The vagaries of NIR penetration depth(s) were described powerfully in the 'Handbook of NIR Analysis' (4.ed) [12], from where a famous quote will help to make explain the situation (p. 434-435). Concerning analysis of a powder mixture:

"*The NIR beam penetrates perhaps as much as 5 mm within the powder mixture. But the radiation that returns to the NIR spectrometer is mostly from the top 2 mm of a typical sample cell. The material in the sample cell may have to be analysed by a reference method (a HPLC method for example or other), which typically has the entire aliquot (extracted increment) volume as its support. If not carefully choreographed, a systematic support volume mismatch error will be committed because the support volumes analysed with different methods (PAT vs. lab reference) are not identical. It also needs to be considered that as the radiation interacts with the top layers, less radiation will be available to interact with the bottom layers of material. The amount of material analyzed may be less in the lower layers of material. In TOS' parlance this is a classic IDE/IEE, here termed a support volume mismatch error in a new disguise in the PAT realm, which did not exist when the classic sampling errors were defined and named in TOS*".

The advent of this type of volume mismatch error will open up for clarification re. the TOS-PAT interrelationships, which are the main present topic.

"*The mass analysed by the radiation may be estimated in some cases, ibid., but is generally not known in detail. Most analytical chemists know exactly the material that is analysed. In NIR spectroscopy, the situation is rather the opposite. Indeed, NIR spectroscopists are spectacularly the most successful analysts that do not know the exact sample mass being analysed!*".

Now, what is the case for NIR spectroscopy can also occur for any other PAT spectroscopic modality for which penetration depth is a function of a.o. material density, composition, physical make-up (grain size distribution), top-bottom self-shielding a.o.

The only exception would by penetrating radio waves, which is much used for volume moisture determination – and, at the other end of the electromagnetic spectrum, very energetic gamma ray Neutron Activation Analysis (NAA) for example, see the article by Kurth in this issue.

5.2 TOS as a contributor to PAT

The Theory of Sampling (TOS) is the comprehensive, necessary and sufficient framework stipulating the principles, unit operations and error management rules necessary to be able to extract a representative physical sample from any stationary lot [1,2,3,5]; the exact same framework guides sampling and sub-sampling in the analytical laboratory as well [6-8]. TOS is comprised of six Governing Principles (GP), five Sampling Unit Operations (SUO) and a set of Sampling Error Management rules (SEM) [5,10,11]. For the purpose of illustrating the interrelationship between samplingTOS and sensor samplingPAT it suffices to introduce the GP#1 and SUO#2, the Fundamental Sampling Principle (FSP) and the sampling process termed composite sampling, respectively. Both these elements were illustrated in Fig. 2. A quick overview of the entire TOS framework is given in [8].

Because there is a physical limit for the possibility of sampling 3-D lots (stockpiles) according to the FSP as lot size go up, it is instructive to note how TOS goes about facilitating how to extract the 'internal' Q increments in practice - TOS's principle 'Lot Dimensionality Transformation' to the fore: The 'impossible-to-sample' 3-D lot is instead placed in a 1-D transportation modus, e.g. placed on a conveyor belt, whence all Q internal increments will eventually be available for sampling when passing muster in front of a suitable process sampling facility (not a cross-belt sampler, but a representative cross-stream sampler – or a fully-fledged PAT solution).

In this fashion Lot Dimensionality Transformation will make all internal increments available for either physical extraction, sampling$_{TOS}$ - or will present these as stream segments readily available for sampling$_{PAT}$. This operation is also what opens up for variographic process characterisation - the most powerful part of process sampling [2,3,5,9-12]; see the article by Romanach in this issue on 'how pharma discovered variographic process characterisation'.

A highly beneficial advantage with TOS is that the basic how-to-sample framework for stationary lots can be directly carried over to the realm of process sampling as well [5,9,10], described more fully in [10-12]. A broad-scoped literature illustrating TOS' role when applied in PAT can be found in [11,12,14-18].

But in the PAT realm, does the PSI design allow the sensor beam to interact with the entire ice-hockey puck volume? This is the (critical) question ...

5.3 Preamble to the key discriminating argument for assessing PAT solutions

All stream increments must be cut in the form of a full slice of the moving, or ducted, material (visualised in the form of an ice-hockey puck) because the material stream is heterogenous: There is no guarantee that a material stream ipse facto has a homogenous cross-section. If/when a sensor is only able to analyse a part of the necessary puck volume, Fig. 3, this is a lack of analytical due diligence. Systematic parts of the series of pucks passing in front of a PAT sensor head, i.e. those parts not intersected by the analysing beam volume, will never be able to contribute to the sensor signal. This means that the sensor signal cannot be representing the full series of cross-sections of the flowing 1-D lot – which is tantamount to saying that the whole 1-D lot is structurally not being represented. This type of beam-limited sampling$_{PAT}$ configuration is not representative. An attempt to illustrate current beam vs. cross-section geometries for many PAT solutions offered (and incorrectly championed) on the marketplace has been compiled in Fig. 7 below.

It is fair to point out that in the PAT community there is considerable debate as to how debilitating the heterogeneity argument above is in practice. For example, it is often stated that in 'many industrial situations' the unit operation 'mixing' has been invoked thereby reducing the heterogeneity of the streaming matter: "sensor results may still give a good indication of the current state of the system, which is not possible with end-of-process testing". While such arguments may be of merit in specific cases (above all typically in the pharmaceutical realm), this is not a justification for liberal generalisations, as there are indeed an almost unlimited number of types of powders .... This is rather a matter for practical empirical justification, enter the Replication Experiment (RE).

5.4 The discriminating PAT argument

The degree to which an implemented PSI creates a sensor beam pathway across the increment cross-section in such a way the analysing volume fails volumetrically to correspond to the full ice-hockey puck geometry, thereby leaving parts of the increment volume without the possibility to interact with the analysing radiation, is a manifestation of a classic bias-generating IDE/IEE. The PAT sensor advantage runs a high risk of being forfeited on the grounds of a volume mismatch alone - unless the specific sensor solution has been thoroughly vetted by a dedicated Replication Experiment (RE). The key argument is pivoting around the volume mismatch between the sensor analysing beam volume (the location and implementation of which is an integral part of the geometrical design of the PSI) and the stream increment delineated simultaneously by the PSI.

The case where a sensor's active analysing volume does not penetrate fully across the cross-section, shown in Fig. 3 as the blue volumes immediately in front of the sensor heads, is likely the largest potential volume mismatch error imaginable. Clearly what the sensor 'sees' in such cases is only a very small part of the fully delineated increment volume. There is manifestly no way the spectroscopic sensor signal from such a PAT solution can claim to be representative of the complete puck volume.

The above analysis of the PSI geometry necessary to guarantee representative sensor signals pertaining to the full cross-sections of moving heterogeneous 1-D flows leads to a definition of what shall be termed the Fundamental Sampling Principle (FSP) for the Process Analytical Technology realm (PAT).

5.5 The Fundamental Sampling Principle (FSP) for PAT

The 'identical volumes' demand constitutes the PAT realm equivalent to the Fundamental Sampling Principle (FSP) for stationary lots. IF/WHEN the analysing sensor volume (radiation footprint x effective penetration dept = ~ radiation beam volume) is not identical to the volume of the full delineated increment geometry (box, ice-hockey puck, orthogonal or warped), there are unavoidably significant fractions of each increment (the sampled flow segment) which is structurally unable to contribute to the sensor signal – which makes the PAT sensor signal biased. Despite many hopeful, but ill-informed claims that powerful chemometric data modelling (specific data pre-processing) can correct for a spectral sampling bias, the TOS explains with scientific logic and force that no sampling bias can ever be corrected for a posteori by any means; the interested reader can find a comprehensive exposé and full argumentation in a recent 'Perspective' paper [7].

The reason behind the 'equal volumes' imperative follows from the fact that all materials met with in science, technology and industry are heterogeneous - it is only a matter of to which degree, and at what scale [1-5]. Heterogeneity constitutes one of two main hurdles for representative sampling (the other is grab sampling, which can never be representative and which is therefore never an acceptable sampling procedure).

5.6 Heterogeneity – the adversary that easily may destroy PAT solutions

There is never a guarantee that a contemporary cross section of a moving flux of matter is homogenous. Material heterogeneity is a 3-D characteristic (at all scales). But when the width-depth heterogeneity of a streaming or ducted material is 'covered' completely by a correct geometrical form/volume extraction of the sampling increments, this is successful process sampling without IDE/IEE. This leaves only the remaining 1-D heterogeneity along the transportation direction to be dealt with – which is exactly the objective of process TOS.

Any vibrational spectroscopy modality being channeled by way of a PAT sensor is subject to the FSP for PAT. In Figure 3, note that a sensor can have a limited penetration depth, oftentimes resulting in what can only be described as sensor grab sampling (blue volumes in front of sensors). It is regrettably fair to say this insight is not widespread within the PAT community, nor in the relevant OEM industry.

To bring home this sweeping statement, Fig. 7 shows many examples of PSI configurations in which the radiation beam pathways are manifestly not identical to the contemporary increment volumes (all examples are culled from [20], but brought here in anonymised form).

5.7 Is all lost? - What can be done?

There are many PSI designs in use as part of a plethora of PAT solutions offered on the market, but many are regrettably afflicted with the IDE/IEE flaws pointed out in this article. Is there any chance some of them can still be used without sampling biases ruining the(ir) complete business? There is both good news (YES) and bad news (NO)!

The capital question: "Is the performance of *this* specific PAT solution [your company / equipment / brand name here] acceptable, or not, can be answered very easily by applying the Replication Experiment facility. This will render an authoritative verdict w.r.t. fit-for-purpose representativity: pass or fail.

5.7.1 Replication Experiment

The Replication Experiment (RE) is described in a number of TOS publications at all levels, e.g. [2,5,7,8,12], of which [5] is likely the most relevant in the present context: DS3077, 2024, (p. 55-57). The simple RE delivers a %-age quality index for comparison with an a priori fixed representativity threshold, below which the particular performance can be declared fit-for-purpose, while a higher index value (higher %-age value) signifies that this quality attribute has been forfeited, i.e. the sampling method tested is not representative. Not testing existing PAT solutions with the simple RE facility is tantamount to not performing analytical due diligence!

5.8 Heterogeneity – good or bad?

The unresolved situations described above are caused by cross-section material heterogeneity which reduces the penetration depth performance of PAT sensors. But, on the other hand, on-line PAT solutions are highly valuable in enabling efficient process/product monitoring allowing inherent heterogeneity along the process transportation direction to be controlled to the benefit of many technological and commercial objectives; these advantages are described in more detail in [9,11,12]. So is heterogeneity a friend, or an enemy?

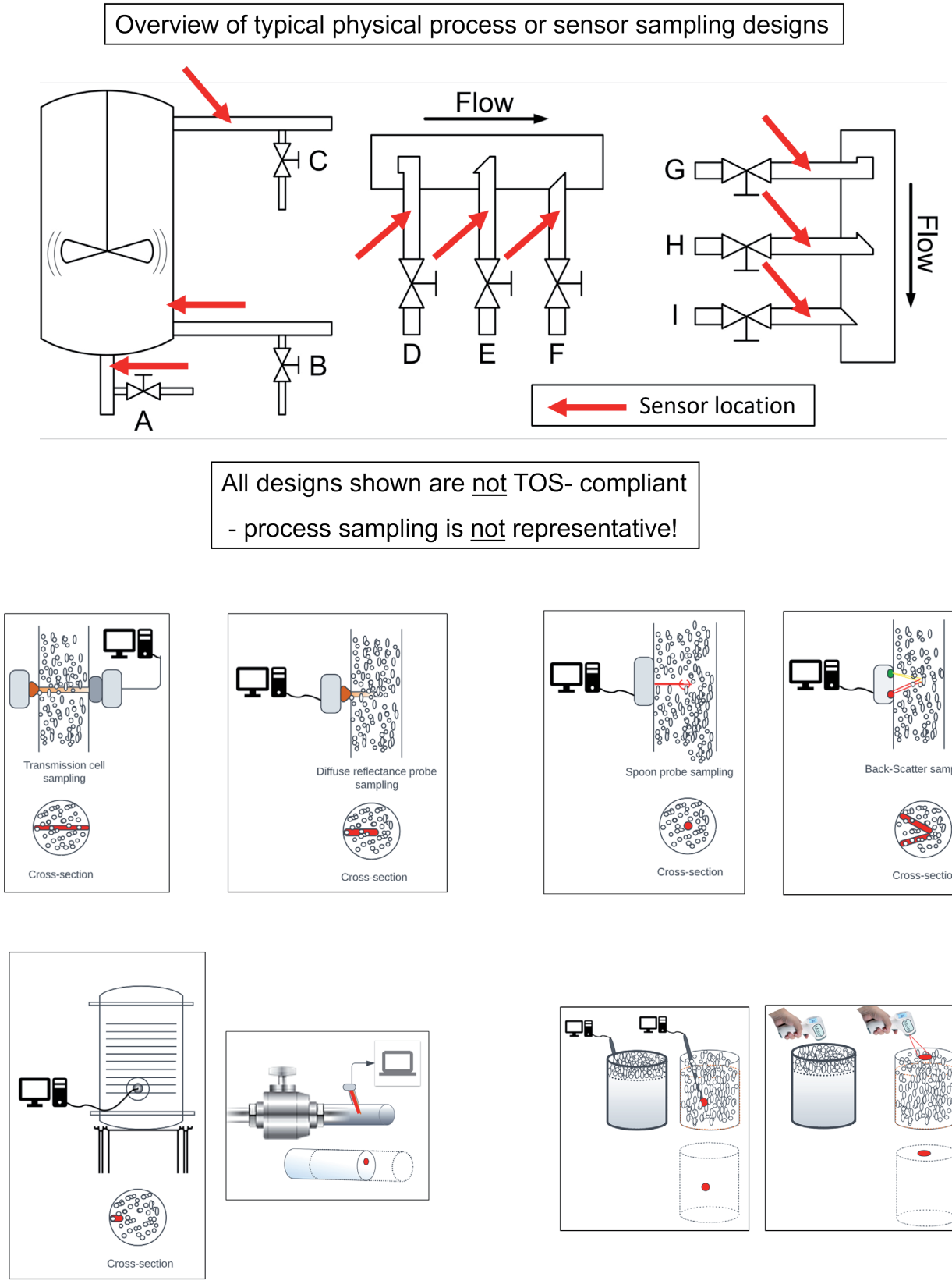


Figure 7: Figure 7 shows a number of beam (red) vs. flow cross-section geometries for PAT solutions offered (and wrongly championed) on the marketplace. All examples are of flawed PSI solutions not facilitating TOS-compliant FSP demands but instead resulting in a variety of sensor grab sampling manifestations compromising representativity to various degrees. Illustrations were originally culled from the internet and here anonymised. *Caveat: these examples are meant for illustration of principles only; no identification of company or equipment brand is intended.*

All materials, process intermediates, products of interest in technology and industry are characterised by a significant (:= not neglectable) heterogeneity, which may differ in nature and magnitude across the infinitely many materials met with in science, technology, industry, commerce, trading, society, but which must never be willingly ignored. For all these the Fundamental Sampling Principle for PAT cannot be ignored, lest a sampling bias be created, which will also characterise the final analytical results. In all these situations, there is no rescue: If-and-when the Replication Experiment does not return the verdict fit-for-purpose, the tested PAT solution does not live up to its representativity obligation. In all such cases there will be practical and indeed painful economic consequences to be faced!

6. Some relief - after all

However, there are redeeming issues that may bring relief.

As heterogeneity goes down, PAT systems merit go up. Indeed, many current PAT solutions and types of equipment were originally designed for expressly manifest low heterogeneity (liquid, two-phase systems, slurries) cases only.

Many current PAT solutions owe their success to the fact that these are only addressing materials with 'practically neglectable' heterogeneity. There is an enormous range and contrast concerning inherent heterogeneity across the almost infinite number of materials for which analytical determination within the PAT scope is of interest (or will potentially come into interest, as technologies develop). Heterogeneity ranges from extreme, high, intermediate, significant, low – to 'practically neglectable'. Baring the last, this article specifically addressed the realm of significant heterogeneity (because this is where the biggest scientific and technological challenges lie) and illuminated the dire consequences if/when sampling is based on procedures and equipment not in compliance with TOS.

Fig. 7 show that a large proportion of current PSI geometries suffer from significant volume mismatch IDE/IEEs. This is an inconvenient truth which is better faced directly than attempted to be sweet-talked away: "My materials are only of (very) small heterogeneity …"; "My materials are (always) very well mixed …"; "In Pharma we are only processing and sampling already well-mixed, low heterogeneity powders …"

While such Hail Marys may be true (in specific cases), they could just as well just represent a tradition for ignoring the hard problems illuminated in this article. Without being subjected to a stringent RE, many current PAT solutions are of inconclusive merit.

Although gas mixtures are often considered to be of very low heterogeneity, gas systems also have special challenges [20]. Sampling and analysis of materials in the gas phase is not covered in general sampling standards and guides, due to the often complex sampling conditions experienced. Most gas-phase materials exist in the region from ambient temperatures (~300 K) to combustion temperatures typically around ~1200 K. Common to both temperature margins, though predominantly for hot gases, or smokes, is the fact that continuous reactions often take place in material moving at high speeds, as well as when samples are cooling down to ambient temperatures, e.g. due to condensation at different due point temperatures, ibid.

7. Going forward

PAT is not a finished, fully developed enterprise, on the contrary. The interesting scientific, technological and commercial challenges mainly lie where forward-looking agents are searching to transgress today's boundaries for PAT application - necessarily often with respect to innovative technological developments trying to deal with increasing material heterogeneity, as more and more new product categories come into view under industry 4.0

But developments are also closely related to continuing analytical developments, which have been left out completely in this article. There is great inspiration to be found in a recent complementary review covering the last 20 years' development as concerns the specifical analytical aspects of PAT [21].

FURTHER READING

An article complementary to the current "PAT" theme: "Sampling for Glaciological "erratic rock" Provenance: the brilliance of Danish Geologist Arne Noe Nygaard" was published in Sampling Science & Technology, April 2025(3), 26-33. Despite its apparently very different subject matter, here can be found a surprising PAT analogue (section 5). The process sampling interface is diachronic, with a time frame between delineation and analysis spanning ~800 years – yet constituting a bona fide PAT scenario!

https://doi.org/10.62178/sst.003.003

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Process Analytical Technologies for Representative Real Time Measurement of Conveyed Flows

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ABSTRACT

Process analytical technologies (PAT) are utilised when continuous knowledge of quality is needed in a timely manner for bulk conveyed flows of matter, usually solid mixtures of highly varying heterogeneities. Reliable, representative monitoring of material quality variability is the target of implementing an online PAT solution, but the material variability itself also has significant effects on the measurement process performance. Many sampling and analytical procedure elements need to be competently designed, managed and controlled for any specific PAT solution.
Conveyed bulk flows consist of materials with characteristics influencing their ability to be appropriately and effectively sampled. The value of the final data is to a large degree determined by its purpose for the PAT system user. This article covers the demands on real time measurement system management where material quality needs to be known with high confidence to influence the technological or industrial processes involved and allow subsequent decision-making. Every process is sensitive to some degree on the nature and specifics of its input parameters. The characteristics that affect online measurement performance cannot always be characterised in a manner like laboratory measurement systems, and various assessment approaches characterise competing system vendors. This article covers some technology opportunities and challenges applicable to conveyed flows that have proven beneficial in this PAT domain as outlined in many case study examples supplied and referenced.

1. Introduction

Mining, minerals processing and many other processes often utilise conveyors in bulk material handling between discrete unit operations. These may include quarrying or mining, simple screening, more complex beneficiation stages, concentrating, recycling, smelting or refining. Process analytical technologies (PAT) can play a role in measuring the bulk material in real time to help monitoring and managing process feed, process performance, and product quality. Sampling may not be an effective solution for quality management if real time and continuous monitoring of quality variability are needed. Sampling may be difficult to implement where coarse material (up to -350mm) is conveyed at high tonnage rates and with highly variable particle size and composition. Effective control can more likely occur when appropriate process analytical technologies are selected (or developed) that provide representative, precise, and timely reliable measurements.

2. How to develop confidence in selected process analytical technologies promising representative real time measurement of conveyed flows

2.1 The Problem

Many material handling situations involve highly heterogeneous material at every particle size scale present. Material 'quality' and its variability have major effects on process performance. How can material quality be characterised representatively to enable the process to achieve a controlled quality at the scale that causes minimal disruption and optimal performance?

The solution should include process analytical technologies that are not affected by the physical characteristics of the material, i.e., quality variability e.g., segregation effects.

1 Scantech International Pty Ltd, Australia

To be representative PAT measurements must comply with the principles stipulated in the Theory of Sampling (TOS), which first and foremost demand that any material component is accorded an equal probability to be included in the support of the physical measurement (physical, or virtual, sample volume). Successful measurements must be shown to be independent from operational handling variability, or sufficiently account (correct for) for variabilities stemming from include e.g., mass flow, particle size distribution (PSD), moisture content, natural or imposed segregation (layering of different materials onto the same conveyor).

Many of the parameters mentioned are the results of upstream processes: 1) PSD as a function of blasting, comminution stages and materials handling, 2) mass flow as a function of how material is handled and whether surging is controlled, or a result of choke feeding, 3) moisture as a function of below ground water level mining, 4) clay content or dust management steps (water sprays), and 5) segregation. These variabilities may be imparted for example due to multiple flows of materials with different characteristics added in a sequence … causing layering, or through natural effects of vibration and movement during conveying. All such 'detracting' variabilities must be optimally counteracted and corrected for a successful PAT solution for one or more focused analytes.

3. Developing PAT technologies

3.1 Compositional and distributional heterogeneity

High compositional heterogeneity is arche-typical in natural geological materials (ores) and in many other bulk commodities in trade and processing technology, which are characterised by coarse particle size (e.g., shredded scrap). Such features will effectively rule out any method that only senses the surface of a conveyed flow.

Conveyed flows are quite effective at self-sorting by particle size, shape, density and parameters affecting aggregation and segregation, such as moisture, or clay content, due to vibration and movement. Fines and more dense components commonly migrate downwards, and coarse particles migrate upwards. This can occur immediately the material is placed on the conveyor belt through particle filtering and chute flow design; this results in induced vertical distributional heterogeneity.

The horizontal composition distribution can also be modified depending on distance material is conveyed, which can result in the same between-particle differences mentioned above.

In many mines the fines are considered as of consistently higher quality than the coarser fraction(s), which are often more competent, being less mineralised rock with lower grades, or vice versa depending on mineralisation style.

The conclusion of the above considerations is that penetrative technologies would be needed to provide even the first opportunity for a representative measurement regime – before even considering which parameters to measure and how to quantify composition. The specific design of the process sampling interface is critical (Esbensen & Sivalingam, 2022).

The measurement parameter of interest (aka 'the analyte') may be aspects of the chemistry, mineralogy or other information that sensors currently are not able to provide, such as ore textures and mineral (spatial) relationships within a particle that affect liberation and recovery processes. Currently there is no technology available to provide a full mineralogical analysis of a flow of rocks through the full depth of conveyed material in real time. This has resulted in application of off-line technologies such as QEMSEM to characterise the material using 'selected' samples (sample selection better be representative). Consequently, existing techniques that penetrate and measure elemental content are the main solution adopted for compositional analysis. The challenge has been to prove they provide representative analysis by preventing biased measurement of any components of the flow. Prompt Gamma Neutron Activation Analysis (PGNAA) and Pulsed Fast and Thermal Neutron Activation (PFTNA) have been the preferred technologies to consider for elemental analysis. Magnetic Resonance (MR) can be considered when only one mineral of interest is required to be measured (this is of course one that is able to be sensed with an appropriate technique).

The suitability and performance of penetrative measurement techniques to characterise the composition of conveyed material can be assessed in various ways. It should be noted that, unlike laboratory technologies that measure samples prepared carefully and consistently through a specified process, conveyed flow is highly dynamic and many variables can affect analyser (process analytical technology) performance.

FACTBOX - Specific analytical neutron activation issues

PGNAA/PFTNA and related neutron or thermal activation techniques are dependent on a number of random processes which include the number and energies of neutrons emitted from a "source" per second, the proportion of neutrons captured by elemental nuclei, generation of gamma energies emitted from "excited nuclei", measurement of the emitted gamma energies by the detector or detectors in the analyser, and the conversion of the collected spectral response through some calibration process to represent elemental proportions. Analyser calibrations use reference spectral elemental libraries to break down the measured spectral response into its components. An analyser is calibrated for the elements known to occur in a material that can be successfully measured, i.e., have a good response to the technique and are likely to be present at measurable concentrations. The analyser calibration can be customised to the expected composition ranges for each element of interest to improve measurement precisions. Each element has a fingerprint, or multi-peak response with peaks over a range of gamma energies at consistent proportions to each other. The consideration of the full spectral response for an element will improve the ability to determine its proportion in the combined response rather than using only its primary or secondary energy peaks. Elements respond differently and therefore some elements are more challenging to measure than others while some do not respond to the technique at all. Elements are continually being added to spectral libraries, and some analysers have unique capabilities, e.g., direct gold measurement, due to their configuration, components and/or calibration software. Theoretical gamma responses are available for most elements but possible recognition by a specific analyser model will vary. Some analysers can detect elements well that others struggle to measure, e.g. aluminium, magnesium, phosphorus, carbon, etc.

The source type and size determine the number and energy of neutrons emitted. Californium-252 (Cf-252) is the dominant source used in PGNAA analysers. Cf-252 produces neutrons with 2.1 MeV energies, which are ideal for this technique. The neutrons are easily thermalised or moderated to make capture by atoms in the conveyed flow more efficient. In this process, high-energy neutrons are slowed down through elastic collisions with a neutron moderator, such as graphite. 50 micrograms of Cf-252 produces about 115 million neutrons per second, about 2,000 times more neutrons than the same amount of Americium-Beryllium (AmBe). Self-shielding occurs when neutrons and gamma rays are absorbed by the material rather than penetrating further into the material and this effect is normally modelled through Monte Carlo simulations so it can be accounted for in the analyser calibration process. This is why higher activity sources are often more appropriate for thicker conveyed beds and why a single pass configuration is used rather than a backscatter process: In a single pass, the source is on one side and the detector array on the other. In a backscatter configuration the source and detectors are on the same side of the material to be measured and consequently may bias measurement to the portion of material closest to the source and detectors which generates a larger proportion of the measured signal. Detectors cannot determine where in the material profile the signals have originated so correcting for such bias is problematic.

Smaller sources have lower activity and emit fewer neutrons. Neutron generators emit neutrons at much higher energies (14.1 MeV) that may reduce the fraction able to be captured by elements as most may pass through the material "uncaptured". The number and type of detectors affect the efficiency of the gamma measurement and resolution of gamma energies into the number of channels being recorded. Digital Multi-Channel Analyser (DMCA) count rate capacity determines how many counts are recorded and accumulated in the combined spectral response over a measured timeframe.

Pulse pile-up occurs when more gamma rays are generated and penetrate a detector crystal than can be counted, so the solution has been to use more detector-DMCA combinations using smaller detector crystals rather than larger detector crystals and fewer DMCAs. The conversion and calibration software plays a major role in the optimal derivation of the final data. If the spectral response is optimised and the highest resolution is available, then elemental characterisation can be improved, and the analyser accuracy and precision can be optimised. The process relies on atoms in the material having approximately equal probability of being "sensed" and therefore the design of the analyser system, the relative position of sources to detectors, and of course the degree of shielding to maintain a safe area around the analyser while operating are important considerations.

Static calibration does not assess the responsiveness of a technology in recognising changes in material composition or compensating for changes in the mass being measured. The mass flow input from a belt weigher is used to tonnage weight spectral responses to ensure elemental proportionality is correct during a measured increment (using a time-based accumulation of spectral response).

Not all vendors are focussed on best measurement capability for various reasons, just like some sampling systems fail to comply with all TOS' requirements. It is not always about building the best performing system as clearly some systems are built to a price point for meeting a particular marketing strategy (i.e., where customers compelled to accept the cheapest tendered price are targeted), while others may be designed without safety as a primary consideration, i.e., safety is left to the client to manage – large exclusion zones, access restrictions, are only safe when turned off, etc. The 'best' performing system may not even be the most expensive. The buyer must develop sufficient knowledge to be able to perform adequate due diligence to select the best solution for them. There are no standards available to assess and directly compare measurement performance and each vendor quotes on a different precision, accuracy or repeatability basis for different analytical measurement periods. Each vendor may also specify that a set of performance estimates is valid at or above a certain belt load (e.g., 60 kg/m) and measurement time. Lower belt loads generate fewer gamma responses, and the configuration of a system will determine the minimum required for confidence in the results. Some systems can measure reliably at belt loads as low as 10 kg/m.

Ideally the analyser will provide certain performances for the desired application given the conveyed flow characteristics: mass flow rate and variability, composition range required to be measured relative to the purpose of the data produced, any required off-line time for calibration or maintenance, operating cost, etc. Measurement time affects the size of the measured increment and whether data can be used effectively to manage overall quality. Very few conveyed flows have consistency in mass flow rate over time. The calibration of an analyser using only static samples of known composition (preprepared standards) can generate repeatability results to assess analytical accuracy and can compare measurements at certain concentrations to claimed accuracies, but these may not cover the full calibrated range or assess responsiveness of the system to normal dynamic conditions (like testing a car under ideal operating conditions and extrapolating its expected performance to reality of all-purpose driving). Off-line static calibrations, such as when the analyser is removed from the conveyor and a standard sample placed on it, offer even less relevant calibration as the conveyor belt composition's dynamic changes (wear over time, or joins or repairs added) and those effects on overall measurement will be excluded. The calibration and performance evaluation processes of the process analytical technology should be understood in the necessary context, so limitations on performance can be used to assess suitability for each specific application.

Dynamic calibration using normal/typical material on the conveyor, in the analyser, under normal operations, enables the impact of dynamic conditions on the measurement to be comprehensively understood and accounted for, to improve analyser performance.

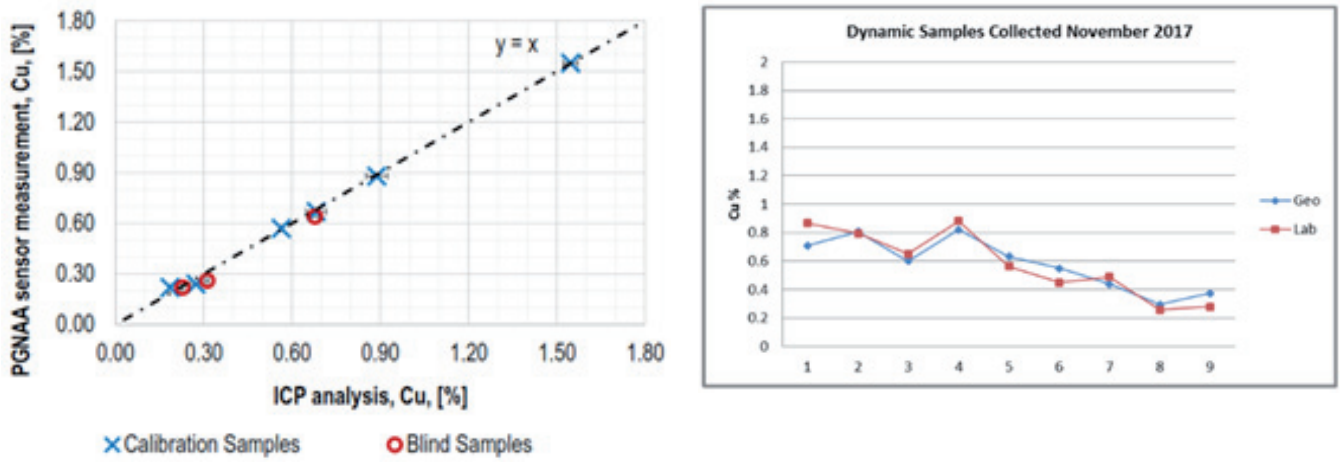
The presence of a suitable physical sampler (must of course be TOS-compliant) or periodically stopping a belt (during scheduled plant shut-downs for routine maintenance), to extract measured material for sub-sampling and assay allows a suitable number of comparison points to be used to validate calibration and measurement performance. This methodology has allowed better precisions than any static calibrations to be achieved over larger compositional ranges in multiple commodities where these systems have been implemented. The ultimate usefulness of all dynamic compositional measurement systems will be reflected in accuracy of the ultimate analytical results with respect to the actual physical material on the belt.

Figure 1 shows how factory test work on a small number of samples can be used to determine approximate measurement performance expectations. The PAT measurements are compared to assayed results for samples and a preliminary calibration developed for the material. This can be assessed using supplied samples without assay information (blind samples) to ensure the PAT can measure the material reliably. In many cases the suitability of the analysis results is a judgment the end user makes based on the measurement performance able to be demonstrated for a technology and its implications for the quality management process. After installation of the PAT the collection of samples from the conveyed flow that are sub-sampled and analysed can be compared to PAT measurements to ensure there is confidence in the PAT data, knowing that some variations between results will be expected due to total sampling error in determining the assay result and instrument errors in the PAT.

The RMSD values represent a confidence level in the measurement and typically correlate well in a suitably designed and calibrated analyser. PAT procurement generally includes requirements for meeting expected performance criteria and an agreed evaluation process should ensure a robust assessment of the PAT.

3.2 Accuracy and precision

Terms used to quantify PAT performance are intended to be objective, however, this is relative to the processes used and different vendors recommend different approaches. "Accuracy" assumes a comparison of measurement performance to an absolute value. To do this a sample is normally synthetically created at a known composition for all important elements to be measured. The repeated measurement by the PAT produces a distribution of results with a mean and standard deviation. The standard deviation is a measure of repeatability at a known concentration. Therefore, the accuracy can be quantified as the difference between the mean measurement and the absolute known composition. Statistical processes applied to the measurement results assume that 95% of the measurements should be within two standard deviations of the mean. Accuracy issues can sometimes be addressed by applying offsets to the PAT results, assuming the difference is always constant, in one direction, however, repeatability may be more random for example because of internal PAT processes in deriving each result. Assessing PAT performance at a single composition is decidedly inferior, as it does not cover the operational range required for the PAT application.



Credit: Nadolski et. al., 2018; used with permission.

Figure 1: Left graph shows factory static measurement on 200kg samples using customer assay data to develop a preliminary calibration with an RMSD of 0.03 %Cu for copper ore for New Afton mine, Canada, and measurement of three blind samples to verify the calibration. Right side graph shows the dynamic evaluation results performed on site with an RMSD of 0.02 %Cu.

Robust assessments require testing and evaluating PAT performance over the range of its intended application. Taking measurements over a range of different materials as presented in the conveyed stream allows comparison of PAT measurements to laboratory analysis based on sampling of the same analysis period for the material. While more resource intensive, this process provides a range of results for multiple estimates of the measured material quality to generate a measure of PAT precision for each element and relative to the composition range in the measured and sampled material. These precisions have been found to be a better indicator of measurement performance especially when the technology is required to guarantee the average quality of a measured batch. The ideal outcome of course is a good accuracy and a good precision in the PAT measurement. Dynamic changes can significantly affect material measurement, and the precision estimates become a better indicator of performance "robustness" where such variability is present, i.e., in most conveyed flows in the resource sector. Accuracies and precisions achieved with PATs are influenced by the amount of signal received per measurement period, resolution of the gamma energies to enable spectral interrogation, weighting of spectral response through mass flow changes, and the customisation of the calibration to the material. Releasing valid accuracy and precision evaluations are a major competitive issue between vendors.

Development of customised calibrations and expansions to element spectral libraries, to include elements additional to the standard ones needed in the "traditional" coal and cement industries where the technology has been applied, has resulted in broader applications for more commodities. The technology has been used successfully for bulk commodities such as iron ore, bauxite, manganese, chromium, phosphate rock and others (physically manifesting a relatively low heterogeneity) as well as more heterogeneous materials such as base metal ores (copper, zinc, lead, nickel), precious metals (silver and gold), platinum group elements (platinum, palladium) and specialised applications (lithium, diamonds).

Calibration is seen as the greatest challenge for obvious reasons. The process analytical technology needs to have its performance calibrated by comparing measured results to known compositions.

CASE STUDY 1: CEMENT INDUSTRY

Dynamic calibration assesses dynamic parameters and can for example be used to monitor and hence guarantee the average composition of a stockpile measured in the longitudinal transportation dimension using a specific analyser. In the cement sector, the GEOSCAN-C is the only product, and Scantech is the only company on the market, to provide composition guarantees for created limestone stockpiles. This provides high levels of confidence the analyser is performing well. For materials such as limestone, the variability is predominantly bimodal (calcium carbonate and quartz are the main compositional components) as the mineralogy is less complex than for many mineral commodities.

As an example, the known composition of a 50kg reference (or calibration) sample will be critically dependent on its full sampling history (it must be primary, secondary and tertiary sampled, sub-sampled and assayed representatively) - and this process must carefully be repeated in an identical fashion for at least thirty samples to cover the full intended measurement range.

The RMSD (root mean squared deviation) can be used as a measure of similarity between two sets of analyses of the same sample set (reference analytical values vs. corresponding process analytical results). The reference assay data is subject to sampling, sub-sampling and analytical errors whereas the calibrated PAT analyser measurement is mainly subject to instrument error (a combination of many smaller components) and errors related to the assay data used in its calibration. Assuming the analyser is calibrated well to the samples, the largest error is how well the samples represent the full flow that an analyser interrogates through its measurement technique.

Dynamic calibration can be improved by diligent sample preparation to minimise sub-sampling errors. The normal site primary sampling protocols are followed by crushing, splitting, pulverising and sub-sampling to the site's standard process or international standards for that type of material or commodity. Dynamic calibration is therefore much more difficult with highly heterogenous ore (such as precious metals with high coarse gold content).

FACTBOX - Validation of sampling vs. analytical error effects

Experience (Scantech) has shown that the sampling error comprises about half the RMSD magnitude (when samples are taken from a period of conveyed flow for comparison to analyser measurement for the same material). Sampling errors have been determined using a duplicate samples approach, and the analytical errors originate from the use of multiple laboratories and different assay techniques for various elements. A typical sampling error evaluation process incorporates operators taking multiple samples from a section of conveyed flow over hours, days or even weeks. Each sample is split and one half sent to one commercial laboratory and the other half to another laboratory. Results are compared to evaluate analytical error. Sub-sampling error is evaluated by splitting samples further and sending these sub-samples to each laboratory. The multiple analyses of the same samples can be assessed using the three instrument Grubbs estimation method (Grubbs, 1948) and when applied to available data often demonstrates the analyser provides a better precision then either of the two laboratories. This issue has been partially addressed using prepared standards with known composition and statically measured by the analyser. As discussed previously, this does not allow for calibration to dynamic conditions seen in the conveyed flow, which may likely have much larger effects on how well the analyser data represents the conveyed material composition. This is a standard process sampling and analysis aspect within the Theory of Sampling (TOS).

For this calibration process it is proposed to utilise a non-destructive analytical technique, such as photon assay (where suitable for the required analytes), so that the full sample size (typically this is equivalent to one metre of belt load) analysed statically in the analyser is removed and crushed to minus 3mm and split into 500gram sub-samples where each sub-sample is assayed by photon analysis and a tonnage weighted average derived for the original sample (Dominy et. al., 2024). Sufficient comparison points (samples) are used to develop what is expected to be the best available calibration for such material.

Ore blending has improved the consistency of process feed quality, reduced plant upsets and improved process performance. Feedback of conveyed material quality to mining operations has improved ore reconciliation and mine scheduling performance. Feed forward of the digital data has enabled process plant operators to modify feed rates, blends and reagent settings to optimise plant capacity and performance. High performance process analytical technologies enable responses in real time allowing for lag time in process changes to take effect.

CASE STUDY 2: GOLD ORE

Despite the high errors involved in sampling gold ores, the GEOSCAN GOLD has been able to demonstrate gold measurement to as low as 0.2ppm and measurement RMSD of 0.25ppm over ranges of up to 5ppm gold. These verification processes have involved meticulous preparation of samples for sub-sampling and assay. At least half of the precision value, estimated using the RMSD, is still expected to be sampling and analytical error, even when 30 or more assay comparison points are used. TOS indicates that most of the total sampling error originates when the primary samples are extracted from the lot. Difficulty in reducing the magnitude of that error suggests that the comparison of PAT measured results to those of correctly selected, prepared and assayed samples may be the best for of comparison for calibration improvement purposes.

CASE STUDY 3: IRON ORE AND BASE METALS

Assmang Khumani, South Africa (Matthews & Du Toit, 2011). Assmang utilises elemental and moisture analysers to measure:

- Mined ore for diversion: approximately 33% of final production bypasses full beneficiation saving around USD 5M per year in unnecessary operating costs. Only material needing beneficiation is diverted to the jig circuits. Ore characterisation studies recognised the potential for this and allowed a smaller plant to be constructed saving significant CAPEX.
- Ore feed to jigs and product from jigs: upgrade factors for different ore types can be well controlled to optimise recovery.
- Product quality to stockpiles: quality of each stockpile is known, so stocks can be monitored in real time.
- Loadout quality from stockpiles to train: allows the tonnage and quality of each train load to be deducted from the relevant stockpiles to manage stocks but also enables that load to be correctly allocated to stockpiles at the port.

The measurement at over 20 locations in the plant using GEOSCAN analysers also allows Assmang to perform real time multi-elemental balance of feed materials from each mine through to product and reject flows to optimise quality management through the complete process. Benefits provided by the mined ore diversion application alone resulted in an effective payback for the equivalent of over 20 analysers across the site in a period of less than one year.

Iron Ore – FMG, WA (Balzan, Beven & Harris, 2015). Fortescue Metals Group applied elemental and moisture analysers to their operations in the Pilbara region of Western Australia to monitor mined ore quality and product quality.

Measurement data is visible by remote access on personal devices. Resource Strategy Director (J. Clout, pers. com.) while travelling in China to meet customers was monitoring product analyser measurement results and noticed low grades being detected on the conveyor feeding the product stockpile. After contacting the site, it was found the mining block had been mistakenly allocated as high-grade ore instead of waste. The cessation of conveying waste onto the product stockpile prevented hundreds of thousands of tonnes of production being out of specification. This proved equivalent to an analyser payback period of one day.

Copper – Sepon, Laos (Arena and McTiernan, 2011. Balzan et. al., 2016). Measurement of crushed ore feed to a mill and leaching circuit for copper production.

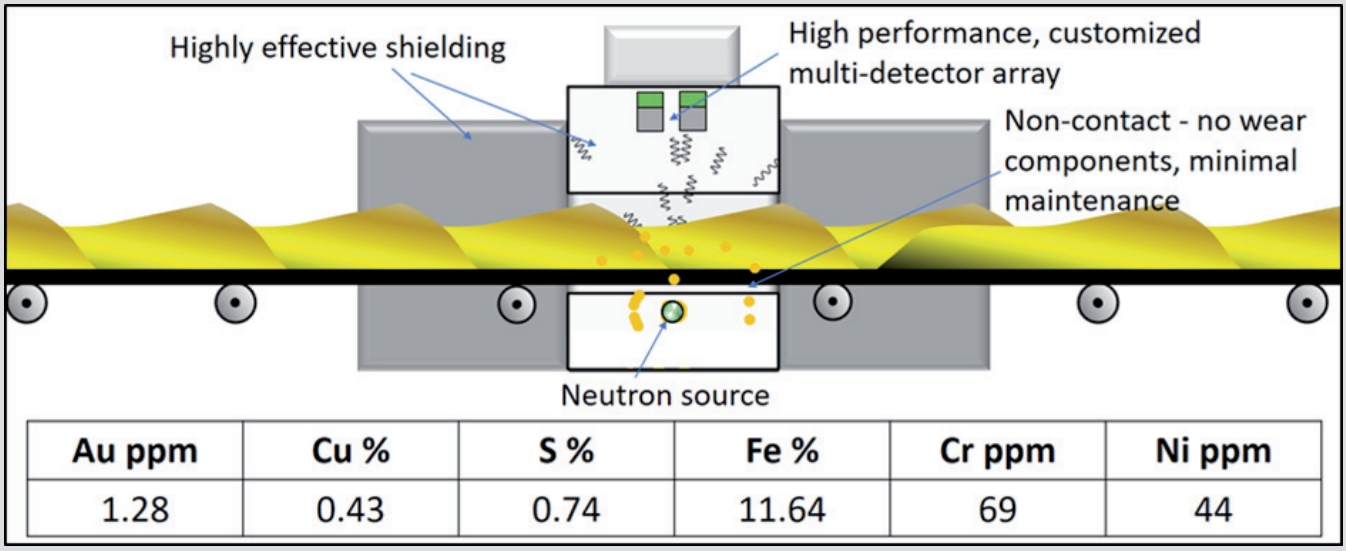
Blending ores from stockpiles is controlled each 30 minutes using feedback from an analyser located after crushing. Heterogeneity within the piles is large and sections of each pile may not reflect the expected average quality. Blending ore from piles averaging 1% copper up to 13% copper allows a consistent copper metal feed rate to the process to prevent exceeding its metal capacity and avoiding direct copper metal losses. Measurement of calcium, magnesium and manganese, correlated with acid-consuming gangue content of the ore, combined with moisture measurement data assisted in controlling acid addition to maintain target pH. The ferric leach process required pyritic material addition from a separate stockpile and its proportion in the feed was controlled using iron and sulphur measurement data from the analyser. Benefits resulted in an analyser payback period of approximately one month.

Lead-zinc – Glencore, QLD (Patel, 2014). Measurement of crushed ore feeding a heavy medium preconcentration plant (HMP).

Feed forward control enabled the optimisation of HMP density cut point control to minimise ore losses and maximise waste reject in lead-zinc ore that previously rejected a fixed 30% feed by volume, irrespective of ore quality. A significant increase in performance was achieved in plant operations.

Gold ore – Newmont, WA (Balzan et al, 2022). Measurement of crushed gold ore from underground mining feeding the Telfer process plant.

Newcrest (now part of Newmont) assisted in the development of direct gold measurement capability using GEOSCAN at Cadia and Telfer sites in Australia. Development of a spectral library for gold as an element was followed by extensive test work to validate measurement results. Since that time gold measurement has been successful at each site; the technology has been installed with measurements achieving precisions of as low as 0.2 ppm gold over calibrated ranges of nearly 5 ppm gold. This development is expected to improve further as better gold assay techniques are adopted to reduce sampling error components. See figure 2.



Au ppm	Cu %	S %	Fe %	Cr ppm	Ni ppm
1.28	0.43	0.74	11.64	69	44

Figure 2: Cross-section through GEOSCAN GOLD high specification PGNAA analyser showing main components and an example of elemental results for a 30 second measurement period; for direct gold measurement over ten minutes.

3.3 Moisture measurement

Moisture content is one of the few parameters than can change during sampling and sample handling. Ambient temperature and humidity can easily affect the moisture of material while being sampled and/or analysed, particularly in hot, dry climates where many mining and processing operations are often located. Free moisture is usually assessed by weighing a sample as supplied, then drying it for a set period at 105 degrees Celsius, and reweighing when dry to determine a moisture percentage. Any moisture losses or additions between the sampling and the first weighing will contribute to the overall measurement error. Moisture can be lost through evaporation simply by disturbing the conveyed flow. Errors can be reduced by capturing a sample into a sealable container before transporting to a laboratory.

Moisture is rarely distributed evenly through a conveyed profile.

Particle size distribution affects the migration of moisture: e.g., finer materials, capillary action and vibration causing water to migrate upwards (similar to tapping a bucket of wet sand), while ambient temperatures, air flow and coarser material results in dryness near the surface while moisture is retained in the finer materials towards the base of the flow cross-section.

The focus needs to be on developing representative measurement techniques to avoid any such obvious measurement bias(es). This eliminates any surface-based measurement techniques because any assumption that a conveyed flow surface, or for that matter the moisture at any vertical position within a flow, represents the average moisture in the full profile is prone to large errors, indeed suspect in the extreme. Continuous full depth measurement is possible using microwave transmission if carefully calibrated to the material and moisture range.

The full width and depth of a flow cross-section is not necessarily covered by the technique due to the lens shaped measurement volume and surface water accumulating at the edges (in the gullies where the material meets the conveyor) and may thus not be fully represented in the analysis, violating against TOS' imperative demand for a complete stream slice (Esbensen 2022).Still this technique has proven more reliable for moisture measurement than many others when effectively calibrated.

Not all materials are suitable for the application of microwave transmission moisture measurement, so sometimes alternative radiometric techniques need to be used. These tend to include collimated beams which are targeted at the deepest part of the flow, and hence they may not provide the lateral coverage to give representative results, although continuous measurement has proven to correlate well with average moisture over short, measured parcels. These approaches have been successfully applied to measurement of moisture in coke and magnetite concentrates. The application on less heterogeneous materials such as metalliferous concentrates, results in very precise moisture measurement particularly when excessive moisture (literally flowing on top of the conveyed material) is absent.

Moisture analyser calibration is a crucial element to ensure that compositional results are indeed representative. Sealable plastic bags with a known weight of dried site material allow moisture content to be adjusted over a desired range and the analyser calibrated to known contents. Mineralogy may affect the moisture measurement technique, so such effects must also be accounted for in relevant calibrations. Looking for universal solutions within the panoply of heterogeneous materials in science, technology and industry is a futile exercise – but dedicated solutions commensurate with specific material compositions and local, site-specific measurement conditions is the only way.

CASE STUDY 4: MOISTURE

In some cases, compositional changes in material that relate to different moisture properties can be determined using an external sensor and the moisture analyser informed on which of a set of pre-validated calibrations to use for a certain material. This approach has been successfully applied to iron ore in Western Australia where the elemental analyser measurements are used to communicate an ore type category (goethite-rich or hematite-rich) to the moisture analyser so the relevant calibration customised for that ore type can be applied for that material parcel. The benefits of such synergies in sensor data (sensor fusion) can apply to many applications of process analytical technologies.

Vendors compete based on science-backed method descriptions, and generous comprehensive calibration and validation information to customers.

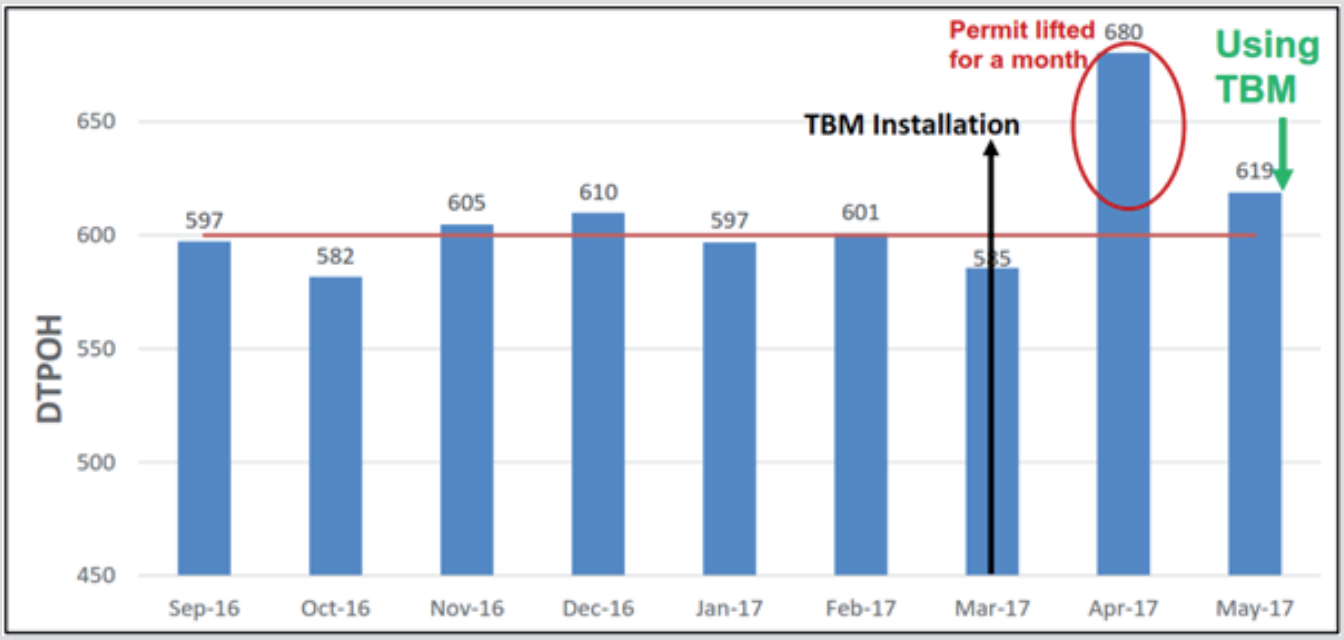
Moisture measurement is critical for dry tonnage determination for metal accounting and ore reconciliation at mines. It is used to monitor TML (transportable moisture limit) in shipping and trucking of bulk cargoes, as well as dust management for conveyed materials. Moisture measurement in dewatering operations can be used to optimise filter or dryer cycle times and throughput to ensure target moisture levels are achieved in bulk product.

In each case there needs to be a high confidence in the moisture data for proper process control responses to be effective in achieving the desired benefit.

CASE STUDY 5: NGM

Cortez Gold Mine (Bozbay & Moyo, 2019) as part of a continuous improvement process.

- The site had a regulatory limit on monthly throughput rate in dry tonnes.
- A conservative moisture factor was used to estimate dry tonnes so that it was kept below the limit, but moisture was not routinely measured with any confidence.
- This represented a huge opportunity for a site producing well over one million ounces of gold per year.
- Due diligence involved multiple vendors, some of which were found to be unable to effectively calibrate their moisture analysers at other sites.
- Scantech ReadiMoist TBM 210 was chosen and within a month of commissioning and calibration the site was able to increase the feed tonnage and stay below the regulatory limit (Figure 3).
- Real time moisture analysis contributed to a three percent increase in annual feed tonnage and gold production, valued at that time at USD 75M per year.



Credit: Bozbay and Moyo, 2019; used with permission.

Figure 3: Improvement of 19 DTOH (dry tons per operating hour) following moisture analyser installation at Barrick Gold Cortez operations in Nevada without exceeding permit limit.

3.4 Particle size distribution

There is no technology currently on the market that measures particle size distribution (PSD) of conveyed material through the full conveyed flow. Particles covering the surface area visible to cameras (or lasers) are normally measured and a relationship with the PSD derived from a sieve analysis of a full cross-sectional segment of the flow is used to extrapolate the measured PSD to that of the full volume for several belt cuts. This type of proxy calibration process has proven reliable in many cases.

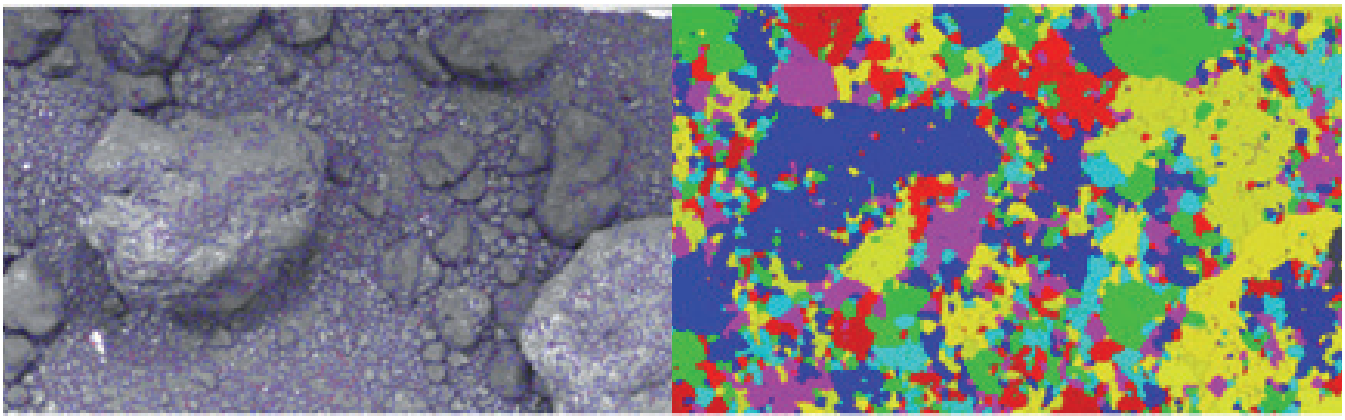
Any number of cameras applied to the flow, even for the falling stream, may not cover the full flow volume, hence achieving a representative PSD analysis remains a challenge. This is not to say there are no benefits in the use of existing technologies.

Most systems on the market have cameras with capability limitations that result in a minimum particle size that is much larger than a client may wish to detect and hence any material recognised as being finer than 15mm, for example, may be classified as "fines".

The camera resolution may also limit the belt speed at which measurement of particles becomes less distinguishable. The application of these sensors may be focussed on the coarser size fractions or detection of "oversize" material to prevent damage to equipment downstream of the measurement location. Hence, the technology may prove fit for purpose for that specific aspect alone. Other benefits of these sensors include their capacity to measure conveyed volume and belt speed sufficiently well to calculate a mass flow to greater reliability than a belt weigher. The sensed PSD can inform the bulk density value used in the mass flow calculation for a given material type. The main error will be through assumptions on a "usual, average" bulk density based on typical fragmentation and specific gravity of the various components. The dangers involved are obvious!

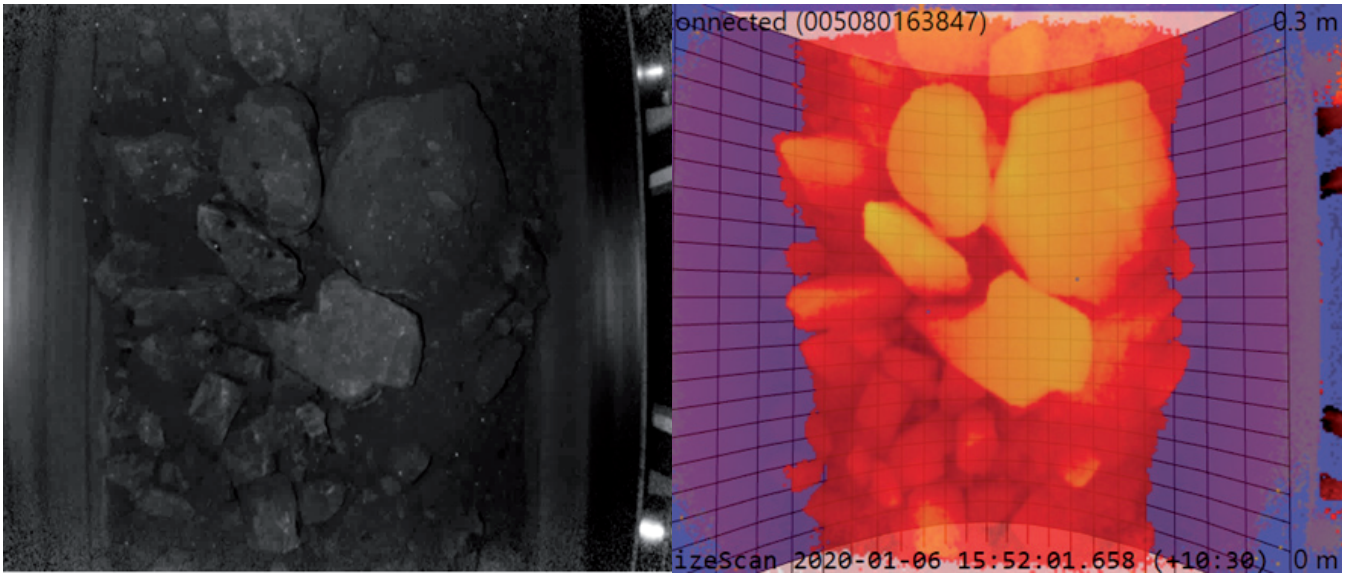
There is a wide opportunity for vendors to compete on the basis of comprehensive sampling -, analytical method - and site-specific knowledge and experience.

The SizeScan is a 3D infrared camera-based PSD analyser using advanced algorithms and was previously known as AGFeed (for Autonomous Grinding mill Feed analysis). It was developed by COREM in Canada (an industry funded research group based in Quebec City) (Faucher et. al., 2015). It was developed due to limitations associated with segmentation software applied to 2D camera images which miscalculated PSD in flows with largely bimodal size distributions because areas of fines with little colour contrasts were considered to be a single large particle and facets in large particle surfaces were misinterpreted as smaller particles (Figure 4). Image processing improvements allowed the images to show elevation associated with surface changes that better characterised particle size (Figure 5).



Credit: Arnaud and Gagnon, 2015; used with permission.

Figure 4: Photo of a segment of conveyed flow clearly showing multiple large rocks and a segmentation software representation of the same image showing incorrect determination of particle size.



Credit: Scantech; used with permission.

Figure 5: Photo of a conveyed flow image and SizeScan analysis clearly showing large rocks and correct determination of particle size despite minimal colour contrast being present in such materials as coke, anthracite and magnetite ores.

3.5 Validation of PAT solutions

All process analytical technology systems and solution are critically dependent on proper calibration and validation. The best way to assess performance is to extract representative samples in full compliance with TOS protocols and comparing the associated laboratory analysis to the PAT analyser data for a period of flow using a minimum of 30 comparison points (an industry developed standard number of reference points); Esbensen (2024). There is today no excuse for not complying with TOS - since 2024 the world has access to a fully comprehensive universal standard for sampling, DS 3077:2024, stipulating all principles and unit operation needed for defensible representative sampling (Danish Standards, 2024).
'Stopped belt' sampling and analysis permits the analysis of a short interval of flow, for example one metre, to be PAT analysed statically and then moved along so it can be removed from the flow for further sub-sampling and assaying (Figure 6). This has been successfully applied where mechanical samplers are not available. A sufficient number of samples needs to be taken for this to be effective in calibration verification.

The most effective measurement of a sample's quality in highly heterogeneous commodities, such as gold ores, may require the removed sample to be assayed in full, such as through a non-destructive offline analysis process, e.g., by photon assay. All of the removed sample of coarse ore can be photon assayed to provide an analysis of the one metre of conveyed flow. This is expected to be the method of choice that minimises sampling, sub-sampling and analytical errors for gold ores.

Other solutions are needed where the samples cannot be taken that are representative of the flow quality. In some cases, there is a need to calibrate analysers statically using samples with known composition which are often finely ground and homogenised. While not preferred, it may be a practical solution that can be used but most emphatically only if/when diligently validated. The analyser measurement of conveyed material should account for the conveyor composition through background measurements on clean, empty belts to remove background signal during normal flow measurement etc. The inability to account for other components of the conveyor belt, such as steel cords or chlorinated content, may, and does, result in poor analyser performances. Robust analyser design and calibration techniques have enabled these conveyor characteristics to be determined and accounted for in calibrations.

CASE STUDY 6: PSD

PSD analysis in a lithium operation in Western Australia ensure any oversize material, which normally migrates to the surface through the conveying action, visible to the camera, is detected prior to material entering a high-pressure grinding roll (HPGR) comminution stage. The HPGR can be damaged if material exceeding a certain size enters the system. It should be noted that a moisture analyser is also used as high moisture material can be detected which may cause clumping and blockage in the HPGR. Both systems provide operational protection from damage and or blockages.

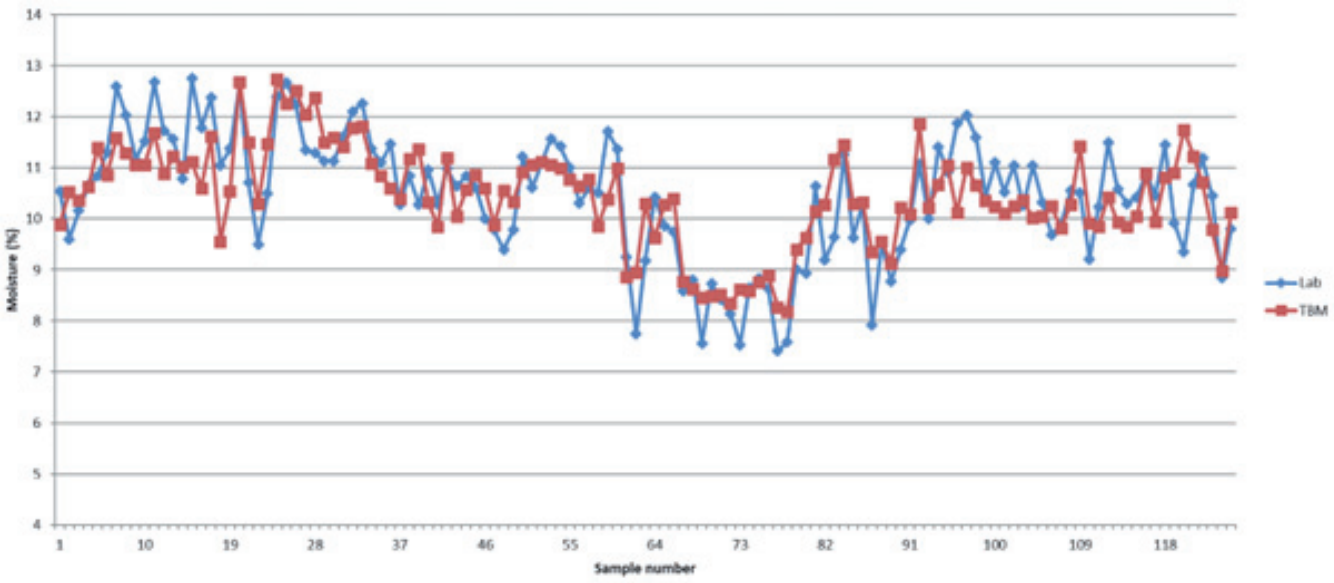
Scantech has demonstrated the ability to distinguish elements such as sodium and potassium in potash ore where chlorine is often present at concentrations in excess of 30 percent. There is here a great opportunity for creative technological improvements.

Experience with various analyser technologies suggests that sampling is least effective for moisture analyser performance evaluation as moisture content can change during a sampling and handling processes and that change (error) cannot be accurately determined. Many operating sites only perform a mass balance infrequently and once a moisture content is determined it is continuously applied as the average moisture factor. No consideration is given to seasonal changes, or dust management applications of water. Moisture content is generally found to be more variable than typically assumed or expected. In figure 7 the moisture measurements are for one-minute averages of flow, and the laboratory results are for samples taken during these same respective measurement periods. The PAT data is an average of a much larger amount of material than that included in the samples intended to represent the same flow.

Elemental composition and PSD are affected to a much smaller degree during any proper (TOS-compliant) sampling processes. Offline sieve analysis is used for calibrating the full volume of a segment of flow to the surface-measured signature for PSD analysers. The type of PSD analysis technology will dictate the frequency of required calibration. The SizeScan system requires only a single calibration after installation.

Credit: Scantech; used with permission.

Figure 6: Example of stopped belt sampling to remove a stream cut from a conveyed flow as fully as possible to compare with PAT measurement data from the same segment to reference laboratory assay results.



Credit: Scantech; used with permission.

Figure 7: Moisture measurement results for hematite iron ore from a microwave transmission–based moisture analyser and laboratory analysis of sampled material showing higher variability in laboratory results.

4. Summary

Process analytical technologies (PAT) are utilised when continuous knowledge of quality is needed in a timely manner for conveyed or flowing streams of matter, usually solid mixtures of significantly very varying heterogeneities. Reliable (indeed representative) monitoring the magnitude and periodicity of material quality variability is the necessary attribute for implementing an online PAT solution – but the material variability itself also has significant effects on the measurement process performance, which must be reduced, controlled or eliminated. Many sampling and analytical components need to be competently designed, managed and controlled for any specific PAT solution.

Specifically, conveyed flows are made up of materials with many characteristics adversely influencing their ability to be appropriately and effectively sampled, although this article argues that the main limitations are engineering and cost.

The value of the final sample assay data is to a large degree determined by its purpose for the PAT system user. This article covered the needs of real time measurement system management where material quality needs to be known with high confidence to influence the technological or industrial process/processing involved. Every process is sensitive to some degree on the nature and specifics of its own input parameters. The characteristics that affect online measurement process performance cannot always be characterised in a manner similar to that for laboratory measurement systems, and this is where various assessment approaches characterise competing system vendors. This article covered the main technology opportunities and challenges applicable to conveyed flows that have proven beneficial in the PAT domain as outlined in many case study examples supplied and referenced.

FACTBOX - Commercial documentation

The application of high specification PGNAA for many elements able to be used as proxies for parameters that cannot be directly measured (e.g., Lithium or Platinum) has resulted in over 140 installations of the GEOSCAN-M or GEOSCAN GOLD in the minerals sector for over a dozen trading commodities. The technology has also found applications in other sectors, such as recycling, where materials may be even more challenging to sample (such as shredded scrap metal, e-waste, non-ferrous scrap). It has been applied successfully to many applications where representative sampling is costly and technically challenging and where calibration solutions have involved extraordinary effort. The effort has proven worthwhile as paybacks on these applications has been as short as a few weeks in several industries. The real time data provided from such systems and the confidence developed by the users has allowed the technology to find many new beneficial applications. The ability to measure representatively over shorter time increments has generated bulk diversion opportunities to remove waste from ore to upgrade plant feed quality, improve plant utilisation, increase metal recoveries and prevent unnecessary processing of material for no value, consuming resources and generating fine tailings.

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PAT: Misconceptions, Blind Spots and Forgotten Basics

By Dusko Kadijevic[1]

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ABSTRACT

Why process understanding, measurement location, and proper sampling are just as important in PAT as our beloved (but often expensive) analytical equipment: the PAT sensors. Here is presented issues that are equally important for optimal PAT solutions as the analytical instrumentation and its performance.

1. Introduction – PAT Is More Than Device Technology

In PAT implementations, identical misconceptions occur again and again in large and small companies. Described below are three typical misconceptions I have encountered many times in practice:

1. The belief that you "already know" the process
2. Neglecting the critical role of optimal measurement location.
3. The technology trap: TOS as a misunderstood foundation.

These misconceptions are closely linked: those who believe they already know the process, tend to plan sampling and measurement location less carefully – and quickly decide on a technology that ultimately does not fit optimally.

1.1 Common Reasons for Choosing PAT

The most common reason to engage with PAT is the desire to replace off-line laboratory analytical samples with direct at-, on- or in-line process measurements. This is of course justified in many projects because it clearly relieves laboratory and operational staff of many work tasks and burdens, improves occupational safety (no hazards from sampling perhaps under dangerous conditions), gives faster analysis results, supplying measurement 24/7 ... so aiming for a PAT solution is often also a powerful driver for automation.

However, before starting down this road, one would often benefit by asking oneself three seemingly simple 'what' questions (Eifert, Erens and Gerlach, 2023):

1. What is the measurement task?
2. What is the core of this measurement task?
3. What is really the core of this measurement task?

Yes – this question is deliberately asked three times, but with slightly different emphasis. Why this repetition?

This question is designed to prevent implementing an unsuitable measurement concept. Analysis of the measurement objective must start here: Why should a specific measurement be taken at exactly this process step (and exactly at this location)?

PAT Insight #1: Before assuming you already know the process, please ask yourself: What is the actual goal — not the technical one, but the value-creating goal? Many PAT projects fail when they chase numbers instead of purpose!

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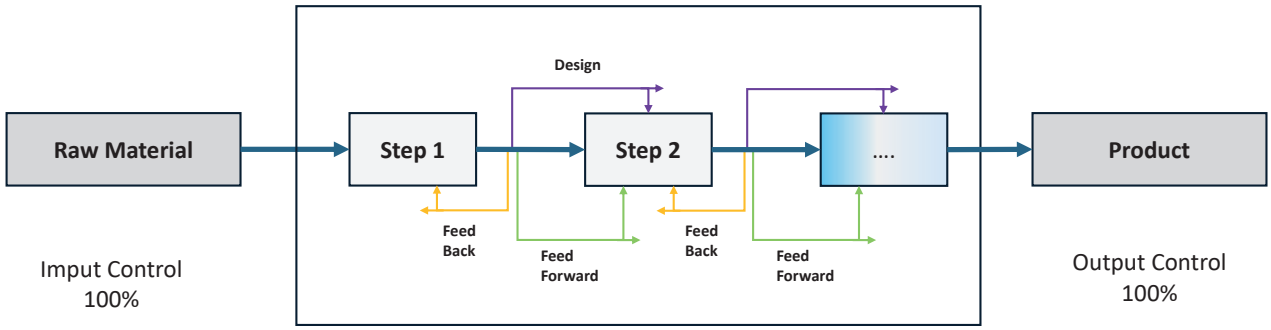

Credit: Kessler, 2001; used with permission.

Figure 1: Graphic illustrating of feedback and feedforward control loops.

2. CPP and CQA in the Context of the FDA Framework (2004)

According to the 2004 FDA Framework (FDA, 2004) Critical Process Parameters (CPP) and Critical Quality Attributes (CQA) can be used as key variables to monitor and control a manufacturing process in real time, for example in order to ensure consistent product quality. The FDA Framework was written for the pharmaceutical industry, but the definitions of CPP and CQA are highly useful across all industrial sectors.

In the context of product specification and property design, it is important that the collected measurement data are used in both feedback and feedforward control loops to automate the process – ideally without operator intervention (Kessler, 2001).

However, this approach is based on an ideal model that presupposes that processes and workflows are comprehensively known and understood.

Field Lesson #1: The smartest PAT engineers choose tools based on fitness for purpose, not on trend or brand. Sometimes a €5000 conductivity sensor adds more control value than a €50,000 spectrometer.

2.1 Dangerous Belief: "Already Knowing" the process

A typical scenario is that of a PAT expert asked whether measurement principle X or Y can be installed at a specific measurement point – usually exactly where laboratory samples have been taken so far. When the expert asks why, the answer often is: "Because there was a ball valve there, or it was the easiest location for sampling for the lab. But when asked where the process model or a proper process understanding would actually suggest to measure, it often turns out that this is not the optimal location. Nevertheless, it often happens that a new and expensive PAT technology is installed right at such a location – sometimes even replicating the laboratory measurement principle 1:1.

PAT Insight #2: Measurement in-line is not automatically real-time. True real-time means that the entire signal-to-action chain — from measurement, through data interpretation, to process response — works without delay.

The problem: The decisive question – whether this location is even suitable for capturing CPP or CQA in real time – is not asked. Instead of defining a measurement strategy, a device is selected directly (all to hastily).

2.2 Unavoidable PAT Uncertainties

In practice it often turns out that the current theoretical assumptions about the process are not correct. Here are three examples of incorrect assumptions:

- There are in practice gas bubbles where none should be
- There are solid sediments that were not anticipated
- There are in fact "wandering" chemical reactions, i.e. reactions taking place along with material transport through the pipeline(s)

Therefore, preliminary tests and trial installations (always including critical validations) are essential parts of PAT planning. Preliminary, trial tests should clarify whether a measurement location and measurement principle work under real conditions, and consequently help avoid costly misinvestments.

3. The Measurement Location Trap: TOS as a Misunderstood Foundation

Representativity and homogeneity are crucial – both in the lab and for in-line, in situ and on-line measurements. The role of sampling 'before analysis' (for laboratory analysis) is replaced by PAT measurement location selection (in-line measurements) or physical sample extraction (on-line measurements). Location errors at this stage can so easily render even the most precise measuring instrumentation worthless.

PAT Insight #3: Combine simple, robust signals instead of overengineering. Clever pairings, e.g., conductivity + density or/and refractiv index often outperform complex systems while saving significantly on cost and maintenance.

The Theory of Sampling (TOS) states that samples must be acquired, or PAT measurement locations selected, allowing PAT sensor signals to represent a complete cross-section of the streaming material.

Otherwise, systematic errors arise causing biased sampling which of course undermine any process monitoring and control (Kessler, 2001; Esbensen, 2025).

3.1 Relevance of TOS Principles for in-line, in-situ, and on-line PAT measurements

In PAT, measurement strategies are typically categorized as in-line, in-situ, or on-line, depending on how and where data are collected with respect to the process. While in-line/in-situ sensors measure directly within the process stream or reactor without physical sampling, on-line systems extract a sample automatically for external analysis.

Based on Table 1 it becomes clear that in-line and in-situ measurements avoid many of the sampling-related errors typical of conventional approaches (IDE, IEE, IPE) and often offer practical advantages. However, their actual superiority strongly depends on the homogeneity of the process material and the representativeness of the measurement location. For example, in poorly mixed systems an on-line measurement with defined sample conditioning may even provide more reliable result.

Interferences caused by gas bubbles or solid particles (e.g., catalysts) can, for instance, increase signal noise in optical measurements, even though they do not contribute to the actual analyte value. In such cases, a sample conditioning step in an on-line system can help achieve more stable readings.

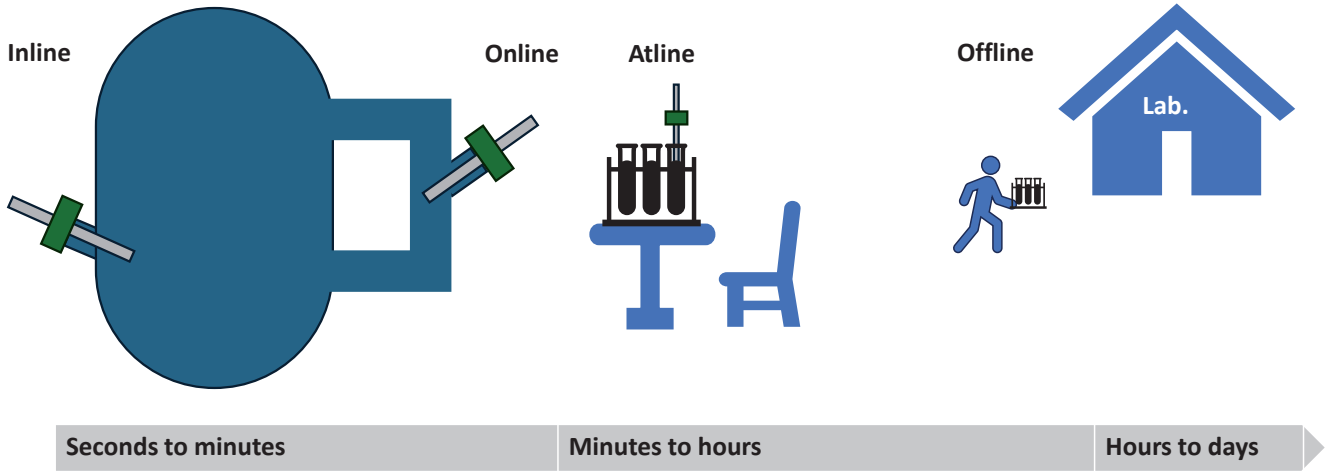

Figure 2: Graphic illustration of in-line, on-line and at-line measurement setups.

Table 1: TOS Criteria and Their Relevance for in-line/in-situ and on-line PAT measurements

TOS Criterion	Definition / Typical Source	Relevance for in-line/in-situ PAT	Relevance for on-line PAT	Comment / Example
FSE – Fundamental Sampling Error	Statistical variance due to limited sampling volume in a heterogeneous system	Partly relevant	Relevant	Sensor measures locally → reduction possible through turbulence or mixing
GSE – Grouping & Segregation Error	Occurs when components are clustered or segregated	Partly relevant	Relevant	Common in multiphase or partially unmixed flows (e.g. suspensions, slurries, melts)
IDE – Increment Delimitation Error	Caused by poorly defined sample or sampling volume boundaries	Relevant	Relevant	Sensor position, sensor field-of-view (FOV) and flow profile critical
IEE – Increment Extraction Error	Error during physical extraction of a sample	Not relevant	Highly relevant	Inline sensors have no extraction step
IPE – Increment Preparation Error	Error during sample preparation, dilution, sieving	Not relevant	Sometimes relevant	Occurs only in on-line systems with conditioning
MEE – Measurement Error	Instrumental or analytical error during signal generation	Relevant	Relevant	Calibration and environmental compensation required
IWE – Increment Weighting Error	Unequal weighting of increments or sub-samples	Not relevant	Partly relevant	In-line sensors integrate over time; on-line systems analyze discrete volumes
TEE – Transformation Error	Error due to non-representative measurement variable	Critical	Critical	Indirect measurement (e.g., refractive index or ultrasonic signal) may not fully reflect the true concentration.

Of course, this modification always comes with trade-offs, such as time delays and additional effort in system design, maintenance, and servicing

3.2 Example from practice: in-line ultrasonic concentration measurement

Inhomogeneities do not only occur in solid mixtures or during powder handling. Liquids, suspensions, emulsions, slurries and gas–liquid systems can likewise present significant challenges for PAT measurements. Local or transient variations in composition, density, or temperature will strongly influence measurement signal quality and representativity and must therefore be considered with great care.

This is particularly relevant for ultrasonic concentration measurement, where the propagation of sound depends on the local physical properties of the medium. The positioning of the sensor and the representativeness of the measurement volume are critical success factors.

Improper placement or flow conditions can lead to biased, unstable readings, especially in multiphase or poorly mixed systems.

Ultrasonic concentration measurement is a physical measurement principle based on the propagation of sound waves in liquids. A transducer emits ultrasonic pulses travelling through the medium, and from the measured sound velocity and signal damping, the measurement system (NB must be suitably calibrated, and validated) can derive quantities such as density, concentration, or compressibility.

This approach relies on well-defined relationships between sound velocity and material properties of the liquid phase. Since the propagation of sound is influenced by density, temperature, and medium elasticity, variations in these parameters are directly reflected in the acoustic response.

In contrast to spectroscopic techniques, ultrasonic methods do not provide molecular information; they measure macroscopic physical properties of the fluid. Because the sensor operates without optical access and without the need for reagents, it is often used for continuous monitoring of homogeneous and two-component liquid systems, for example in pipelines or reactors, where robust, real-time information on concentration or density is required.

Typical sources of inhomogeneity include:

- Gas bubbles: Even small fractions of entrained gas strongly attenuate or scatter the ultrasonic signal, resulting in unstable, biased readings.
- Pressure variations: In zones of reduced pressure (e.g., after valves, or at pipe outlets) degassing may occur (dissolved gases come out of solution), forming bubbles that disturb measurement stability.
- Poor mixing: In areas with insufficient turbulence or incomplete forced mixing, stratification or phase separation can occur, producing locally different concentration profiles.
- Deposits (fouling): Over time, precipitations and sediments on sensor surfaces can further dampen the signal and shift readings.

Installation recommendations from manufacturers reflect these challenges: ultrasonic probes should preferably be installed downstream of pumps. Pumps not only provide sufficient mixing but also increase the local pressure, keeping gases dissolved and minimizing bubble formation. Likewise, vertical installation positions help bubbles escape upward, away from the measuring zone. By contrast, locations directly after throttling devices, in dead zones or at pipe outlets, are especially prone to degassing; therefore, unsuitable for reliable ultrasonic measurement.

4. Manufacturer Guidelines and the Link to TOS Principles

Manufacturers of in-line ultrasonic systems explicitly address the same physical challenges described by the Theory of Sampling (TOS) — i.e., avoidance of Fundamental Sampling Error (FSE) and Grouping and Segregation Error (GSE) effects, which is caused by local inhomogeneous material and/or irregular process conditions.

The sampling and service documentation provided by ultrasonic equipment manufacturers shows critical awareness of the effects from the Increment Extraction Error (IEE) and the Increment Preparation Error (IPE).

A typical example would be from the company LiquiSonic® which instructs users to log both the controller timestamp and the distance between probe and sampling point when taking reference samples, ensuring time-aligned comparison between in-line readings and laboratory data. This structured correlation of field and lab measurements strengthens traceability and enables identification of localized inhomogeneities that might otherwise remain undetected in continuous operations.

Figure 3 shows typical installation guidelines highlighting suitable (green) and unsuitable (red crosses) positions for in-line ultrasonic concentration measurement. The reliability of the measurement strongly depends on sensor placement and local material and flow conditions. Positions (1), (3), (4), (6), and (9) are considered unsuitable, as they are prone to degassing, turbulence, or stagnant flow (e.g., near valves, outlets, or at the reactor bottom). Positions (2), (5), (7), and (8) are recommended, as they provide stable flow and opens up for optimised reproducible conditions. In particular, position (5) downstream of the pump ensures sufficient mixing and pressure to minimize gas bubble formation.

These installation principles (as illustrated by the company SensoTech), reflect general good practice for achieving stable and reproducible ultrasonic concentration measurements in pipelines and reactors.

Overall, these manufacturer's approach embodies key TOS principles in a practical, industrial context: ensuring representative measurement conditions, documented traceability, and active error monitoring. Such design features transform the TOS from a theoretical sampling framework into an operational quality assurance tool for modern PAT installations.

While these measures significantly reduce the main sampling-related errors (FSE, GSE, IDE), TOS' principles cannot be fully fulfilled in in-line ultrasonic measurements, since the sensor head here only probes only a local section of the process stream rather than the necessary complete tream section (see further below and in another article in this issue (Esbensen, 2025).

4.1 Example from practice – on-line gas composition measurements

An on-line gas measurement probe was installed immediately after a pipe bend. The results were precise – but not accurate, sometimes too low, sometimes too high.

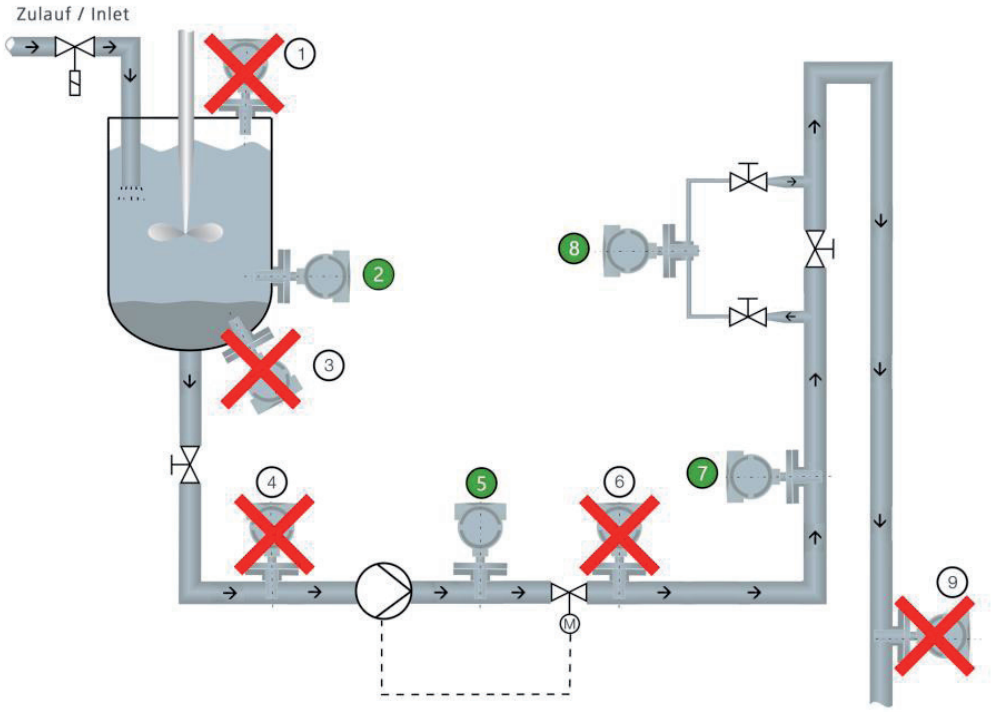

Figure 3: Recommended and unsuitable installation positions for ultrasonic concentration sensors (adapted from SensoTech GmbH installation manual).

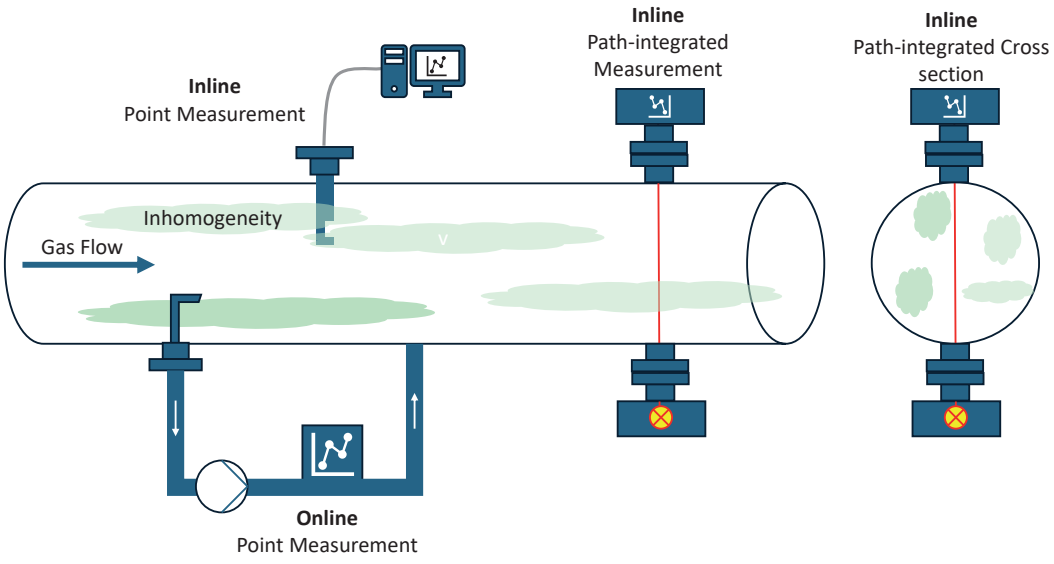

Figure 4: Illustration of on-line and in-line PAT sensor installations in an inhomogeneous gas/gas mixture stream.

The reason was that flow velocity locally influenced the gas composition, i.e., there were actually inhomogeneities even though this was a supposedly well-mixed gas flow. Indeed focused investigations revealed formation of channled flow patterns. The remedy in this case consisted in installation of up-stream static mixers, and of a different PAT probe at another measurement location. Lesson learned (a reflection of a much broader general problem): An in-line measurement would not have been better here because most in-line probes are also point measurements. Very many in-line methods, e.g., laser spectrometers, pH meters, focused PAT probes result in 'point measurements' - essentially optical grab samples (Esbensen, 2025) - that are completely unable to represent a complete stream segment (see another article inthis issue). An early overview of TOS as applied to gas and gas mixture characterisation was given by Larsen and Esbensen (2020).

5. Business Case Aspects

Selection of incorrect, non-optimised measurement location not only runs a high risk of significant wastes the equipment budget, but also invites unnecessary risks for:

- Production time losses (through misinterpretation)
- Production of scrap (due to inferior or incorrect process/product control)
- Additional costs (for unnecessary modifications)
- Reduced trust in PAT performance

The last point in particular – trust – must not be underestimated. Once lost, it is difficult to rebuild trust in technical solutions, making new projects harder to initiate, or even impossible (before a new management is in place – which is a much bigger project to undertake).

5.1 Practical Example – Costly correction of measurement location

In a chemical company, new measurement technology was installed to capture a critical quality parameter directly in the process. The investment for equipment, integration, and commissioning exceeded €80,000. The measurement location was initially identical to where laboratory samples had previously been extracted – without detailed verification of whether this location was truly suitable also for continuous process monitoring. The company was only interested in a specific analyte occuring in one of the mixture components.

After commissioning the following became clear:

- The medium at this location was not sufficiently well mixed. But this heterogeneity did not raise alarms, because it did apparently not impact on the manual sampling, as the analytical aliquot was taken after phase separation in the lab.
- Occasional gas bubbles in the product stream severely compromised the optical measurement principle. Again, this was not an issue for the subsequent manual sub-sampling for the analytical aliquot.
- Temperature fluctuations were greater than expected, significantly impairing measurement stability.

This all resulted in significantly varying, unreliable measurement results, indeed they were unsuitable for process control. After weeks of troubleshooting, the measurement point was moved several meters to another location with (more) uniform flow, (more) stable temperature, and no air entrainment. Additional modification costs surpassed €20,000.

Field Lesson #2: A short pilot (or perhaps an instrument on loan) would have revealed this problem instantly. Precautionary early testing first — even with soft sensors or simple devices — prevents expensive rework later.

5.2 How could this have been avoided?

- A targeted preliminary study of the planned new installation condition would have been an easy option e.g., focusing on flow simulation and visualization, temporary test measurement with a mobile device
- Automatic locating a new PAT measurement point at exactly the same existing lab sampling point is very often dramatically inferior to determining the optimal position analytically (for the probe and the process).
- Interdisciplinary coordination is always good, as between process engineering, plant operations, the laboratory and the PAT team - to validate theoretical assumptions against real process conditions.

Such preliminary checks can save not only the extra costs but also weeks of project delay.

6. QbD and Regulatory Frameworks

In the pharmaceutical industry, measurement strategies are an integral part of validation. Quality by Design (QbD) and Process Analytical Technology (PAT) are closely interlinked – both require a solid process understanding before any technology decision will be made.

Regulatory authorities, such as the FDA and EMA, expect that the criteria for measurement location selection and data usage are documented in a traceable manner. The QbD concept requires that all CPPs and CQAs are identified, comprehensively understood, and monitored with appropriate measurement approaches already during the development phase (FDA, 2004).
This last demand makes eminent sense: only those who understand and fully model a process from the outset can later operate reproducibly within a defined "design space."

In practice, however, this is often more difficult. Subsequent changes to measurement points, sensors, or process parameters in a validated environment are laborious, requiring extensive documentation, testing, and re-approval.

This is sometimes called the "validation pain" – the effort can be so high in practice that necessary adjustments are delayed or avoided entirely: double jeopardy! (Dahlgren et al., 2020).

The idea, of course, is to understand the process so well before validation that later changes are unnecessary. But often "all theory is grey." Even carefully planned QbD approaches encounter unexpected effects, deviations, or new insights in reality, forcing adjustments.

PAT can help here, but only when measurement points and principles are chosen so that they continue to deliver relevant and usable data even when requirements change.

PAT Insight #4: Early PAT during Research and development reduces validation pain later. Once a system is validated, changes are expensive — learning early allows simpler, cheaper sensors in production.

7. Forgotten Basics: Soft Sensors and Data Integration

In addition to classic measurement technology, using existing process data combined with operators' vast and valuable experiences offers an often underestimated way to gain additional insights and improve process control. This is where so-called soft sensors come into play.

Existing process data and the empirical knowledge of operators can be used to calculate virtual measurement values.

Surprising insights often emerge when talking to operators and specifically asking how they steer production at present.

Examples:

- Calculation of viscosity from physical measurements (temperature, torque, rotational speed, power consumption of mixers and pumps)
- Moisture estimation (from dew point and temperature measurements)
- Concentration calculations (via material balance models)

PAT Insight #5: More data do not necessarily mean better control. A signal must be representative, robust, and interpretable — otherwise it only adds noise.

7.1 Control charts as a complement:

Data obtained via soft sensors, or direct measurement, can be effectively monitored with control charts. Control charts are statistical process monitoring tools used to distinguish between random (common-cause) and systematic (special-cause) variation in time-series data. They are based on continuous plotting of measurement results (or derived quantities such as model residuals) compared with statistically defined control limits, typically set at ±3 standard deviations (UCL) from the mean (Control Line: CL). Deviations beyond these limits, or persistent drifts within them, indicate that a process may have shifted from its expected state (in a trending or in a more fluctuating fashion).

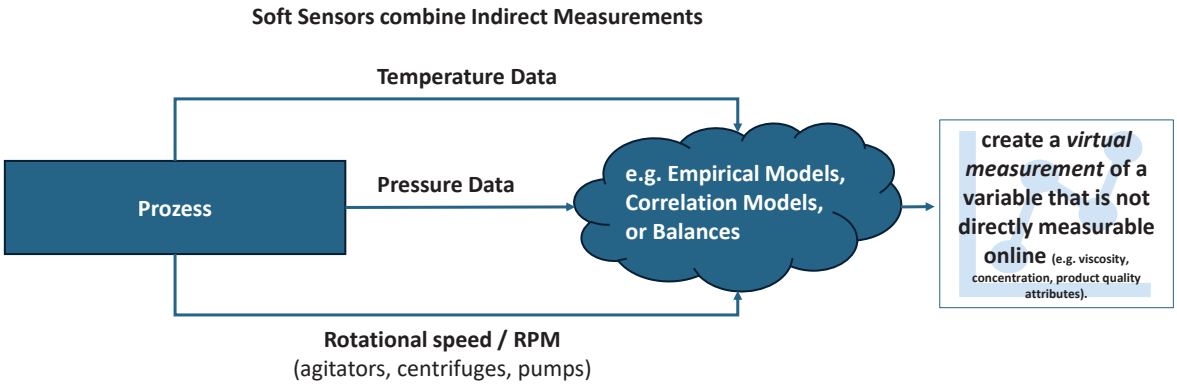

Figure 5: Schematic illustration of the soft sensor principle.

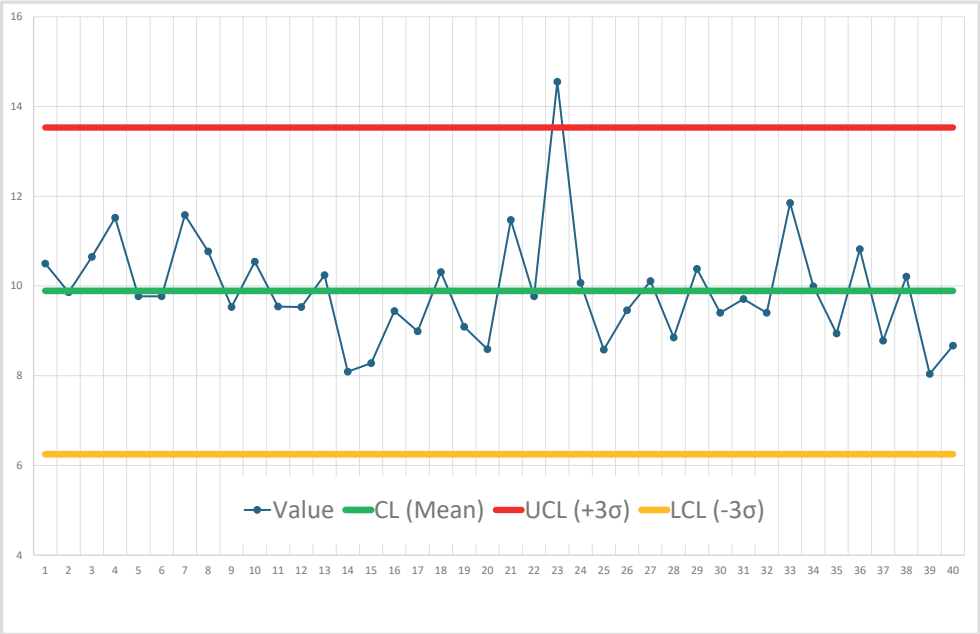

Figure 6: Illustration of control chart, typically set at ±3 standard deviations (UCL) from the mean (CL).

Several types of control charts exist, each suited to different data characteristics:

- Shewhart charts visualize pointwise deviations and are well suited for detecting sudden changes or outliers.
- CUSUM (Cumulative Sum) charts integrate small deviations over time, enabling early detection of gradual drifts.
- EWMA (Exponentially Weighted Moving Average) charts smooth short-term variability and emphasize recent data, which makes them effective for trend monitoring in continuous processes.

Data obtained via soft sensors or direct PAT measurements can be effectively monitored using such charts. They provide not only current values but also reveal trends, process shifts, and emerging deviations, quite often before they become apparent in conventional quality checks. In this way, control charts support both early process intervention and validation of long-term measurement stability. But there is also an important limitation: The quality of soft sensors and derived control charts depends directly on the quality of the data and its representativity (Esbensen, 2025). With the right methodology and motivated data analysis, meaningful monitoring values can often be determined surprisingly well and can be statistically substantiated.

7.2 Examples

In emission analytics, CUSUM (Cumulative Sum) control charts are frequently used to track slow drifts in analytical systems. They provide early indications of the need for necessary maintenance, recalibration, or instrument adjustment well before threshold limits are exceeded. Their continuous nature makes them particularly suitable for long-term monitoring of sensor stability and process performance.

Control charts are also increasingly used within Process Analytical Technology (PAT) frameworks to ensure the robustness of inline and online measurements. A common approach involves Multivariate Statistical Process Control (MSPC), where data from spectroscopic sensors (e.g., NIR, Raman, or UV/Vis) are condensed into principal components (PCA/PLS). Control charts based on principal components help distinguish random variation from systematic drift, and provide a quantitative basis for model maintenance and recalibration decisions.

Furthermore, CUSUM-type charts have been explored for monitoring residuals from chemometric prediction models, improving the sensitivity for small shifts in complex data streams.

Many examples can be found in the chemometrics textbook (Al-Rashed, Al-Mutairi & Al-Attar, 2019).

7.3 Checklist – Measurement Location Planning

A well-thought-out measurement location plan determines whether a PAT system will later be able to deliver useful and reliable data. Before a decision is made, the following points should be clarified:

- **Clear definition of the goal and benefit of the planned measurement**
  Has it been specified why the measurement is to be carried out and how the data will be used (distinguish between monitoring, control, release, prediction, alarm)

- **Are CPP/CQA known and measurable?**
  Are critical process parameters (CPP) and critical quality attributes (CQA) for the specific application clearly defined, described and directly/indirectly measurable at the planned location?

- **Flow and mixing conditions as well as process engineering constraints?**
  These topics include temperature/pressure profiles, phase states, gas bubbles, sedimentation, installations, dead volumes, delays in bypasses, cleaning/fouling, materials, safety issues

- **Theory of Sampling criteria fulfilled?**
  Ensuring representativity for in-line and on-line measurements are de rigeur. This includes sub-sampling, sample preparation, return of residual sample material. Data quality is a critial attribute spanning three domains, see Esbensen 2025.

- **Validation concept in place?**
  The following must always be planned a priori: calibration, validation, verification, acceptance criteria, maintenance, drift monitoring, data integrity, change control.

Field Lesson #3: No sensor is truly calibration-free. Factory settings and self-monitoring can help, but verification and periodic validation remain essential, especially when process data drive important and critical decisions (e.g., release decisions in pharma) (FDA, 2011; EMA, 2015).

8. What does all this mean in practice?

A measurement only has real value if it effectively contributes to monitoring, control, release, or optimization. Target outcomes can include shorter cycles, lower energy consumption, higher yield, less raw material usage and/or less scrap, and consistent quality.

A salient practical example would be the use of an in-line NIR or laser diffraction device (PAT) in the mixing segment of an emulsion production, providing an early correlation with droplet size distribution. This information allows agitator speed and dosing profiles to be adjusted during batch production instead of waiting for laboratory tests. The result is more stable quality and less rework. Another example would be regulation of an evaporator stage, not simply by temperature but directly by solids content using conductivity or NIR signals. This enables the same product quality at lower temperatures, saving energy and reducing thermal damage of the product.

The goal of a measurement should therefore never just be "to produce a number," but to enable a model or control strategy that leads to improved process management and resource use.

Equally important is to define CPPs and CQAs correctly and not to confuse them with final product specifications. CPPs and CQAs relate to what is required for process control. Final product specifications are critically important for product chances on the market, but they often do not help for production or manufacturing control.

A polymerisation example will illustrate this well: final molecular weight is determined in the lab and is decisive for, say, product release, but it cannot be measured in-line. Instead, an IR band correlated with monomer conversion can be measured in-line and used for process control. The final CQA remains a release criterion, but the CPP-related IR signal allows stable operation and fewer off-spec batches.

9. Flow, mixing, and process conditions are further decisive factors

Local inhomogeneities, installations, and operating states can massively influence the measured value.

One example was the above-mentioned gas probe installed behind a pipe bend that produced local inhomogeneity streaks caused by secondary flows. Only after installing a static mixer and relocating the sampling point to before the bend were stable values obtained. Another case would be an in-line NIR probe, disturbed by gas bubbles in the product stream. The solution was a physical bypass with degassing, a modified installation position of the window, and a slight pressure increase.

Dead volumes and delays in by-passes can also cause practical problems.

An on-line analyser with twelve meters of sample tubing had a residence time of several minutes, making process control impossible. Only by shortening the tubing and increasing the flow rate could the the delay time be reduced to under the required one minute.
Similarly, temperature and pressure fluctuations can cause spectral shifts if not accounted for in calibration, or stabilized by tempering the measuring cell. Finally, fouling and deposits on windows are a frequent reason for drift and upsets. Flushing, anti-fouling coatings, or Clean-in-Place (CIP)-capable designs are essential in these cases.

10. TOS thinking – is good for PAT

Applying correct TOS principles is often the decisive point in practice but is sadly, frequently neglected.

For example, a NIR system may be calibrated with laboratory samples extracted after filtration, while the in-line probe interacts the unfiltered stream. The result is likely to show significant systematic errors and shifts. The correct approach would be calibration with process-representative samples from the same environment. Alternatively, an online system with controlled sample preparation can be implemented to ensure that the measured stream closely reflects the true process composition.

In gas analytics, another example concerns isokinetic sampling: if the sampling velocity does not match the flow, certain particle or droplet fractions are over- or underrepresented in the extracted sample volume, leading to the dreaded sampling bias, dreaded because it can never be corrected for. In emulsions, sampling itself can change the sample when pumps or lines introduce shear which may alter droplet size distribution, an illustrative example of an Incorrect Extraction Error (IEE) in the PAT domain. In all cases, the rule is clear: contemporary process representativity is mandatory, otherwise even the most expensive measuring devices are worthless.

Validation must not be considered only at the end of a project. Acceptance criteria, test plans, and proof procedures should be carefully defined from the start of any PAT project. For an in-line sensor, this means predefining the desired limits for measurement uncertainty, recovery, stability, drift, and failure rates already during the planning phase.

The system's entire lifecycle – from initial and ongoing calibration through regular verification and maintenance to spare parts strategy and data integrity – all must be most carefully documented a priori. Any changes to the process or product recipes must feed back and influence validation through meticulous change control.

Typical pitfalls in practice include carrying "laboratory thinking" into the process, i.e., calibrating with non-representative samples, or simply reusing laboratory sampling points as process measurement locations. Equally problematic are long or poorly designed by-passes that cause delays and dead volumes, as well as ignoring temperature and pressure effects, or underestimating fouling. Countermeasures include calibration and validation with process-representative samples, flow- and mixing-aware placement of measurement points, minimizing dead volumes, considering temperature and pressure effects in the model, planning cleaning strategies, and integrating maintenance from the beginning.

The numerous practical examples above show that these issues are not merely of theoretical importance.

11. Conclusions

Some of the most often forgotten basics, misconceptions and blind spots regarding PAT system design and implementation were presented. PAT does not start with buying a 'powerful analytical device' in isolation - but instead starts with analysing the measurement task, the measurement location, and the physical and chemical process reality. Only in this way can robust, economical solutions be created that enable appropriate, improved process control.

The conclusions are clear: Before any procurement, three decision gates must be passed.

1. Is the technical suitability proven, i.e., representativity, flow and mixing conditions, T/P effects, delay time, and is maintainability demonstrated by tests and pilot trials?
2. Is the economic benefit shown and compelling, i.e., are the expected savings in scrap, energy, or time versus CAPEX/OPEX, environmental impact calculated realistically?
3. Is validation and routine operation conditions ensured with the desired bracketing attributes, i.e., calibration, proper validation, verification, acceptance limits, alarms, data integrity, and change control sufficiently documented?

Only when a system passes all three decision gates will procurement be worthwhile. Only then will the likelihood be high that a new PAT solution will genuinely and effectively contribute to improved process control.

FINAL THOUGHT

Even the best PAT setup fails without ownership. Every successful project has a PAT champion who connects proper planning, QA, TOS, lab, maintenance with production and logistics — and keeps the system alive after commissioning.

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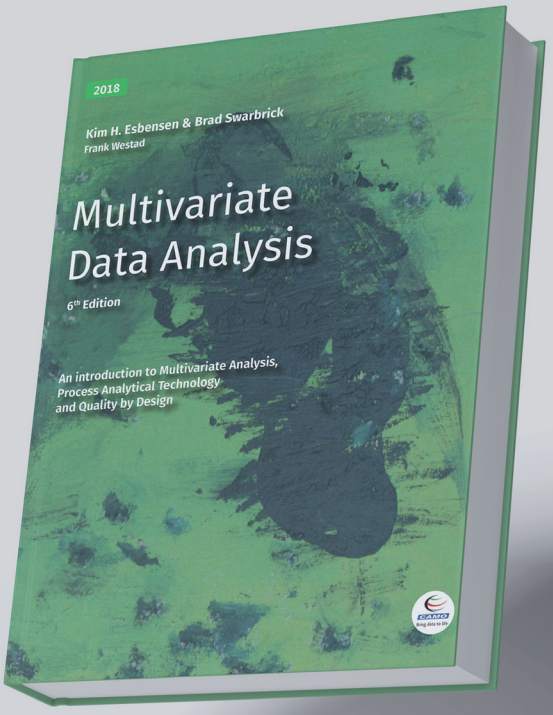
Multivariate Data Analysis

by Kim H. Esbensen and Brad Swarbrick

An introduction to Multivariate Analysis, Process Analytical Technology and Quality by Design



- A smooth and user-friendly introduction to chemometrics and MVA, both from a theoretical and practical point of view
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The Role of Chemometrics in Establishing PAT Prediction Models for Analytical Concentration Determination

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ABSTRACT

The implementation of Process Analytical Technologies (PAT) has not been possible without a symbiotic relationship with chemometrics – multivariate data analysis and modelling. This article complements the context for this issue of SAMPLING SCIENCE and TECHNOLOGY (SST), 'The PAT issue', by introducing a compact brief of chemometrics: defined as the extraction of information from chemical data for the purposes of making informed decisions, especially when integrated with PAT, where quality decisions are made in real-time on the current state of the process. Using predictive chemometric models, changes can be made to the process so as to minimise the risk of deviations and out-of-specification (OOS) material.

1. Introduction

Implementation of process analytical technology (PAT) is not plug'n'play! As is evident from the articles presented elsewhere in this issue of Sampling Science and Technology, only in the rarest of cases concerning extremely low material heterogeneity will direct insertion of a PAT probe into a process stream result in the acquisition of representative spectral data. This article gives a perspective of what happens on the 'other side' of a successful PAT sensor implementation, where raw spectral data has been generated for the development of data models for prediction of analytical concentration (calibration of analytical instrumentation). For this ultimate PAT step chemometric multivariate calibration (and validation) come to the fore.

Chemometric data models have been instrumental for the successful development of PAT (see several other articles in this issue). The standard, proven chemometric data analytic approaches include methods such as Principal Component Analysis (PCA), Multiple Linear Regression (MLR) and Partial Least Squares regression (PLS) that are not only simple in application but are easily interpretable and can be validated to any contextual level.

This latter in deliberate opposition to current Artificial Intelligence (AI) and Machine Learning (ML) approaches that are wonderfully efficient data-wise, but which mainly work in the dark. By their nature these approaches are not amenable to proper validation.
A comprehensive introduction to chemometric MVDA is Esbensen and Swarbrick (2018), in which all relevant aspects regarding MVDA data models are presented in an authoritative context, including the critical sampling and model validation issues in full (chapters 3 and 6 respectively).

For all PAT implementations, there are a number of prerequisites that must be met with:

1. There must be a physico-chemical relationship between the PAT signal and the analyte(s) of interest.
2. There must be a 1:1 volume correspondence between the sample(s) characterised by the PAT sensor (either on an extracted sample or as a spectral signal [X] pertaining to a relevant stream segment) and the aliquot used for reference analysis [y]. [X,y] are the complementary matrix/vector data needed for the generation of chemometric models.

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3. The samples used to generate a calibration MVDA model must span the greatest relevant range of analyte concentrations as defined by the PAT objective; for example, if a regulatory specification requires the range 75-125% of the target analyte concentration, the calibration sample set must span this range as well (analytical range and internal validation).
4. The calibration data set [X,y] must fit the relevant form of the MVDA model (for example, a straight-line fit for a linear model). If the model shows non-linearities, these must be addressed using an appropriate and interpretable set of pretreatment data transformations and/or by using an extra number of data analytical components.

The model must generate reliable prediction concentration results when applied to new samples which are independent of the calibration set (test set, or external validation).

It is of key importance for steps 3-5 to be reliable, that steps 1 and 2 are complied with without exception. There is an alarming recent trend where newcomers to PAT/ chemometrics are looking for automated ways of generating models - and ditto: automated way of validating model performance without putting in the effort to understand what a particular model is doing and why the particular preprocessing method applied is relevant.

There is a vast range of preprocessing methods available for this purpose, but their use requires considerable insight and experience. Even more alarming is today's indiscriminate use of non-linear, AI and Deep Learning approaches, which will fit any data set, but provide little or no interpretation insight, hence they have little or no scientific value.

Before providing examples of the way PAT has been implemented and the perils of poor sampling, the next section defines a compact roadmap for chemometric data modelling based on sound sampling practices. A first set of introductory literature references for newcomers to chemometrics can be found in (Wold, 1995; Esbensen and Swarbrick, 2018), augmented by four historical and general background references (Martens and Næs, 1991; Massart, 1997; Adams, 2004; Höskuldsson, 2024).

2. A Concise Introduction to Chemometrics Methods

Chemometrics is not application of mathematics – chemometrics is the prime data analytical tool for extraction of information from chemical data. While there is a mathematical component involved, chemometrics is very much also dependent upon knowledge and experience about spectroscopy, chemistry and pattern recognition - all bought together such that essential subject-matter interpretations can be made.

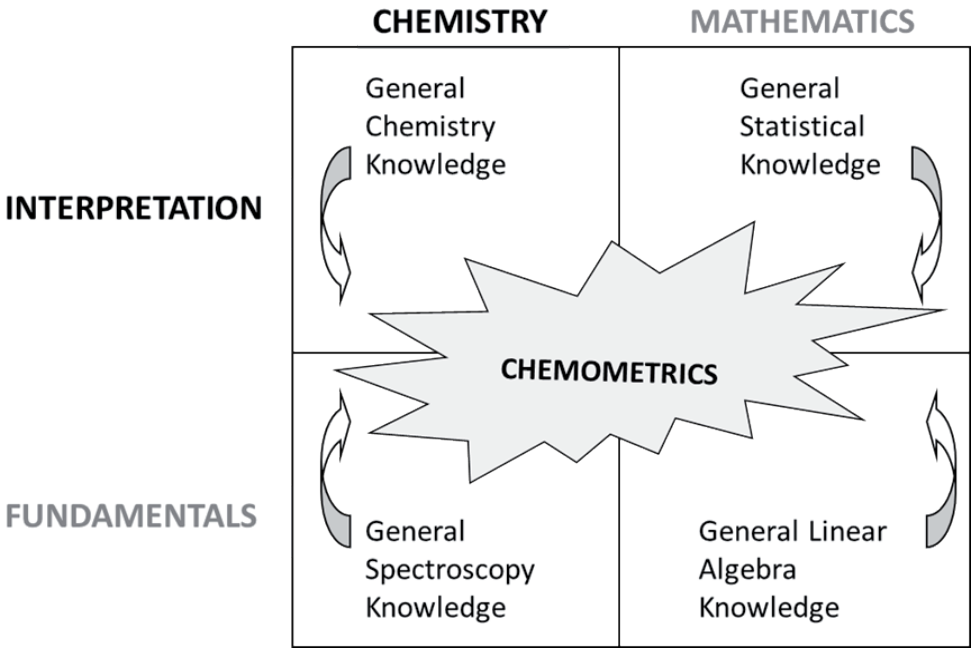

Figure 1: Chemometrics was born as a branch of chemistry concerned with the analysis of acquired data and ensuring that experimental and empirical data contain the maximum information [3]. Since its inception in 1972 chemometrics has developed into a general data analytical approach long since transgressing the boundaries of chemistry.

Figure 1 provides an infographic of how the disciplines of chemometrics come together to achieve the goal of understanding data structures embedded in data tables (data matrices), e.g., [X] and [X,y].

For the present compact perspective, chemometrics can be sub-divided into three main areas (Esbensen and Swarbrick, 2018; Martens and Næs, 1991; Massart, 1997; Höskuldsson, 2024; Adams, 2004):

1. Exploratory Data Analysis (EDA): This type of analysis is used to detect trends and patterns in spectroscopic and other types of multivariate data. Data may typically come from discrete samples generated at different locations or may be data generated over time from a process line.
2. Regression Analysis: Predictive models are generated from paired spectroscopic and 'reference' data [X,y] acquired on the same sample. In this way, the calibrated spectroscopic data [X] can generate many more predictions [Y] = [y1, y2, y3 ....] compared to physical sampling and sending samples to a reference laboratory.
3. Classification: The uniqueness of spectroscopic and other multivariate data for grouping into specific sample classes is used to develop discrimination models that can classify new, unknown samples w.r.t. known training classes. Training classes are bound by statistical limits, therefore providing a level of confidence to the predictions.

No matter which approach is used, chemometric data models follow the same foundational principle of partitioning data into a systematic structure part (the information part) and a noise part, Fig. 2.

In the general case of EDA, the data are partitioned into the structure part, i.e. groups, trends etc. and a noise part that the model cannot explain.

In the Regression/Classification case, a functional relationship between X- and Y-Data is established. The better fit of the data to the model, the less noise influences the model. However, if there is no subject-matter 1-to-1 information in the data, the noise part will be inflated and the resulting model performance will necessarily be poor.

Even if there is a lot of information in the data, or there is a strong relationship between X- and Y-Data, if proper sampling methods were not effectuated when generating the samples, the resulting analytical data will inherently be more influenced by noise than need be. In such cases, chemometric modelling will partition most of the data structure into the noise part – and the potential for generating a useful and acceptable model is often forfeited. It is never a good idea to ignore the good sampling imperative! A good primer for connecting the sampling, analysis and the data analysis realms can be found in (Esbensen, 2025a; Esbensen,2025b).

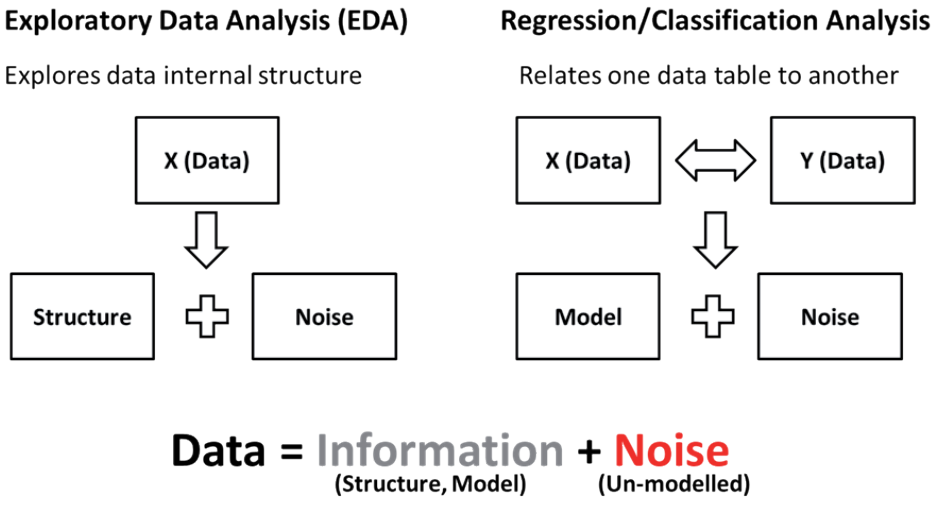

Figure 2: The general structure vs. noise decomposition assumption behind all chemometric data modelling

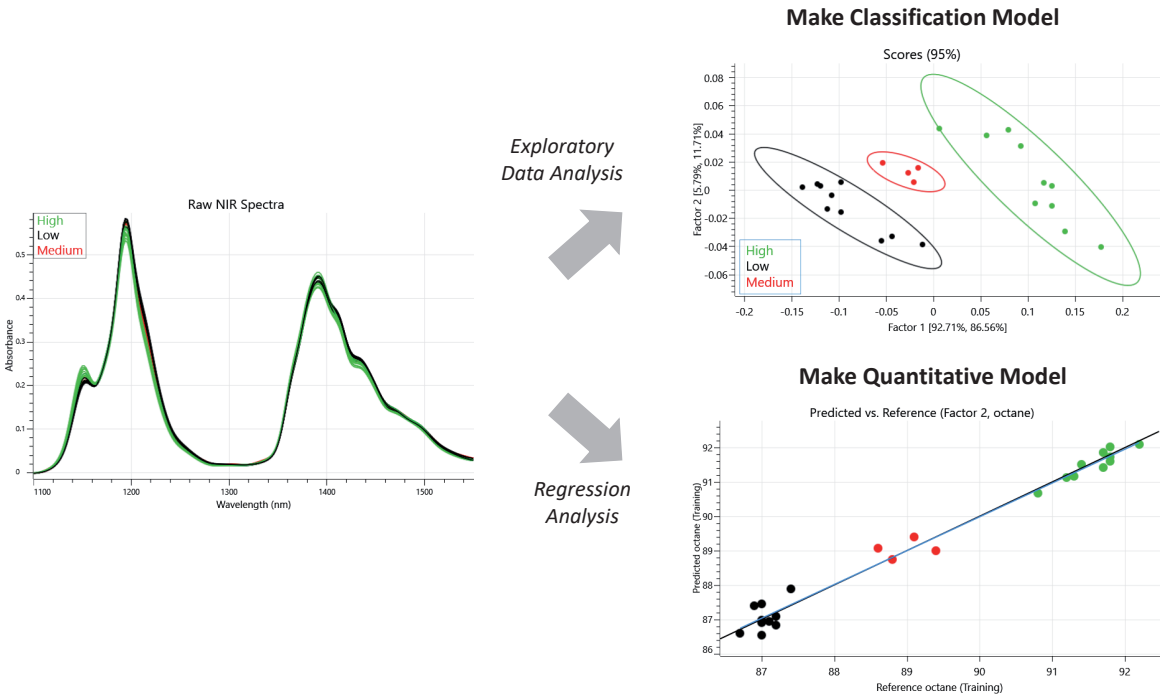

Figure 3: Generic example showing how spectroscopic data can be decomposed into structural patterns for classification or regression prediction. A multivariate chemometric model detects many feature the human eye does not, which is why these methods are called latent methods.

Fig. 3 shows illustrative examples of the regression and classification/EDA objectives in terms of chemometrics' key graphic performance facility, the so-called scores plot and the predicted vs. reference plot, which are common to methods such as PCA and PLSR. Full introduction in (Esbensen et al., 2018; Esbensen 2025a).

This brief chemometric overview has not considered the preprocessing, interpretation, optimisation and validation efforts which are also required to generate a reliable analytical prediction model.

In general, for most data analysis objectives, there is no need to look for more complex, non-linear, or more advanced methods to "sort through the rubbish" - if sampling is addressed and the right PAT technology is chosen(Esbensen and Swarbrick 2018; Esbensen, 2025a; Danish Standard, 2024).

The prime hallmark of chemometrics is the insistence of proper validation of all data models of whatever type (Esbensen and Geladi, 2010). Recently the place and role of multivariate data modelling/chemometrics was described in a broader philosophical perspective (Esbensen, 2025a; Esbensen 2025b).

Chemometric models can, in some sense, be viewed as a subset of Machine Learning (ML) models but by including the important aspects interpretability, problem-dependent outlier detection and proper validation they are in a class of their own. Chemometrics was founded in 1972; referral can be given to a bonanza of introductory literature developed over more than 50 years (Martens and Næs, 1991; Massart, 1997; Adams, 2004; Esbensen and Swarbrick, 2018; Höskuldsson, 2024; Danish Standard, 2024; Esbensen, 2025a; Esbensen 2025b) and further references herein.

3. Five "R's" of Chemometric Model Development

One of the most influential documents used as a guideline for the development of reliable analytical models was developed by the International Conference of Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) in the Q2(R2) (ICH, 2008) document.

This document, entitled "Validation of Analytical Procedures" and its latest counterpart ICH Q14 "Analytical Procedure Development" (ICH, 2022) have been referenced in many other regulatory documents, including the European Medicine Agency's guidance on the development of near infrared (NIR) spectroscopic methods (European Medicine Agency, 2014) and may be condensed into the four R's of analytical development.

1. Repeatability: Can the same aliquot be remeasured in a short time period and generate predictions that are not significantly different, typically at the 95% confidence level, or with a relative standard deviation < 2% (PAT instrument analytical precision).
2. Reproducibility: Typically relates to the transfer of a method from one PAT instrument to another. Reproducibility is an assessment of prediction accuracy and precision with respect to the aliquot mass.
3. Robustness: Does the PAT approach generate statistically similar results when small, but deliberate changes need to be accepted regarding the full measurement system (lot-to-aliquot). This is partly also an assessment of the reliability of the sub-sampling system implemented to generate the stable raw spectral data.
4. Reliability: Typically relates to the precision and accuracy statistics of the calibration model and the method ability to predict new samples (external validation).
5. Representativity. This the forgotten "R" which is the focus of this SST issue. Representativity relates to the support mass/volume for PAT sensor signals (can either be defined w.r.t. an individual stream segment (increment) or the full length of the streaming material batch, see (Esbensen 2025a, Esbensen 2025b) for a detailed discussion). Representativity of any analytical result must point back to the original target material or lot.

PAT representativity must be seen in relation to the positioning of the sampling sensor in the process stream and the ability to establish a representative process sampling interface, see Esbensen in this issue. This last point is of overwhelming importance for PAT, typically requiring ~75% of any PAT method development efforts. This also reinforces the old saying, "Garbage in, Garbage Out". If the data being generated are not representative, one cannot expect the chemometric model to perform miracles.

4. The Chemometric Model Development Roadmap

Armed with this information and a systematic approach to method development, the workflow in Figure 4 summarises the development effort required to generate reliable, robust and representative chemometric analytical prediction models.

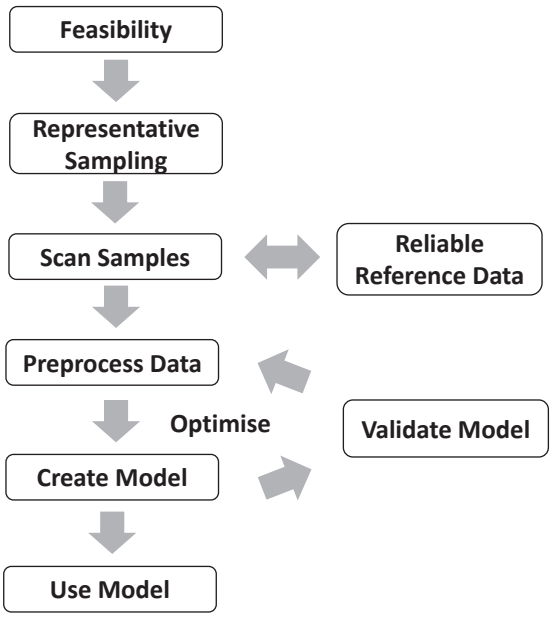

Figure 4: Generic workflow for developing reliable chemometric prediction models.

A brief substantiation of Figure 4 is as follows.

1. Feasibility Study: It is not necessarily an easy choice to find a candidate sensor, considering the very many sciences and applied fields which are opening up for PAT, e.g., biology, pharmaceutical, metallurgy, geoscience (minerals, commodities, ores), processing industry. A feasibility study is used to verify that the signal from the selected PAT sensor is indeed related in the physical, chemical or subject-matter sense to the analyte(s) of interest.
2. Representative Sampling: Is the PAT instrument located correctly in the process, and does it generate a response that is a true representation of the aliquot delineated by the process sampling interface (Esbensen in this issue). Be aware that it is not always possible to extract the exact same sample from the process that was characterised by the PAT sensor (volume mismatch error introduced in Esbensen this issue). Representativity is very much also related to the procurement of sample data sets (chemometrics: training and validation data sets) used to extend the range of constituent analytical min/max values.

3. Sample scanning: This is the critical element in analytical due diligence: proper optimisation of spectral acquisition parameters. This is the core of the analytical domain (Höskuldsson, 2024). Failure to optimise analytical instrument parameters will lead to the generation of imprecise raw spectral data, which cannot but influences negatively on the relevance and power of chemometric prediction models.
4. Reliable Reference Data: There must be a strict 1:1 reference sample-to-analytical-aliquot correspondence as any misalignment or disconnect between the two will result in imprecise and biased data. The reliability of the reference method [y] must also be established to generate the Standard Error of Laboratory (SEL) value. Without a critical evaluation of SEL, the precision and accuracy of the final prediction model cannot be properly assessed.
5. Preprocess Data: Preprocessing is *not* a supermarket of methods used in random combinations to generate a 'cleaned up' dataset. Proper application of preprocessing is intimately related to both spectroscopic type and wavelength region. Preprocessing is used to minimise the effects of residual spectral acquisition effects and can often be helpful in bringing out more clearly the subject-matter (e.g., chemical/biological) information in the acquired data. N.B. Preprocessing is no substitute for representative sampling!
6. Establish -, Validate -, Optimise Model: This is the iterative cycle of proper chemometric model development where fine tuning is applied to wavelength region selection, or to preprocessing methods such that the minimum number of components/factors are used in the final model and so the calibration and validation prediction statistics are as close (in the statistical sense) to the SEL as possible. Ideally one would prefer complete similarity, but this would be dependent upon successful elimination of all sampling, sub-sampling, all spectral acquisition errors, as well as all data modelling errors – a complete impossibility for the degree of complexity met with in technological and industrial data sets. The optimisation step results in a model that, when applied to a new, external sample set, will generate predictions that can meet the validation criteria defined for the model, often a minimum prediction error measure is used.
7. Model in use, Model Maintenance: The only way to improve a(ny) model in practice is by learning through its application. This is the Model Maintenance stage and must be implemented as a lifecycle model (Flåten, 2018). The model maintenance stage allows a user to identify whether process changes have occurred that result from identifiable causes, e.g., raw material changes, or observable changes that may indicate the need for PAT instrument maintenance, or changes pointing to the need for re-calibration and renewed qualification. This stage is obviously where informed competence and the largest possible experience with model use in practice will be of key importance.

5. Chemometrics for PAT - in practice

The following two examples illustrates the result of not following the above approach, i.e., of neglecting the principles of Good Data Modelling Practice (GDMP) outlined above.

5.1 Consequences of incorrect PAT Sampling for Chemometric Models

An important distinction: PAT is not about bringing the quality control laboratory to the process (an often-used euphemism) but is about PAT's ability to assess the current state of a process or a product. In this sense there are PAT implementations that work in an at-line capacity (Esbensen in this issue) where a specified number of representative samples are drawn from a process and measured at predefined intervals.

5.2 The Divided Sample Dilemma

This type of sampling error has been observed in so many PAT implementations that it is worthy of some consideration. This type of mistake typically occurs when newcomers to PAT are sold an instrument with the prospect of it generating more results so that 'faster and more informed quality decisions' can be made.
In this case, a specimen (grab sample) has been taken from the factory floor and sent to the QC laboratory for reference analysis (primary sample). Here a sub-sample is taken (alas also by grab sampling) from the primary sample which is used to generate reference values [y] (secondary aliquot). Then a second sub-sample is drawn from the primary sample for generating data on the at-line PAT instrument; this is done by grab-sampling.

This setup results in just about a maximum of errors committed:

Mistake 1: The primary sample is a grab sample; it is therefore not representative of the lot.

Mistake 2: The two sub-samples (one of which in this case is actually the analytical aliquot) are also grab samples (grab sub-samples), and thus neither are representative.

Mistake 3: The 1:1 reference-to-PAT [y-X] correspondence is lost as the sub-sample used for reference measurement (y] is different from the one used to acquire the sensor signal [X].

The result of this fatally misguided approach typically results in decreased precision in the fit of the data to the model due to the inflated uncertainty induced by the various sampling errors. Figure 5 shows the impact of this practice on the resulting chemometric model.

The regrettable consequence behind this situation is that both PAT and chemometrics get a bad name and the typical advice provided by non-experts is to acquire more samples and add more components/factors to the model to improve precision.

This is poor advice indeed as chemometric modelling and preprocessing methods cannot model the heterogeneity- induced sampling errors.

Figure 6 illustrates the performance of the same prediction model after making the following four changes to the methodology,

1. Acquire a proper primary sample from a representative sampling device. The Theory of Sampling (TOS) to the fore, see e.g., (Masser, 1997; Esbensen and Swarbrick, 2018; Hökuldsson, 2024; Esbensen in this issue).
2. Generate the analytical aliquot(s) using a representative sub-sampling procedure and equipment (Massert, 1997; Esbensen and Swarbrick, 2018).
3. Scan the analytical aliquots on the PAT instrument using optimised spectral data acquisition parameters.
4. Acquire the reference data on the same aliquot used to generate the PAT sensor data.

Figs. 5,6 illustrates how the only way to improve model precision is through due diligence in the pre-analysis sampling/sub-sampling domain (Esbensen, 2025a). It is fair to state that this understanding is not all-persuasive in today's PAT realm!

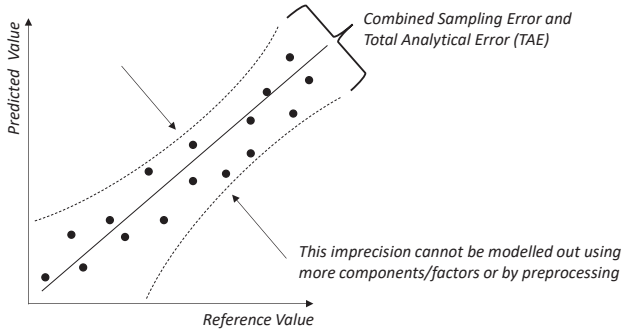

Figure 5: Impact of non-representative sampling/sub-sampling and the loss of the 1:1 reference-to-PAT correspondence.

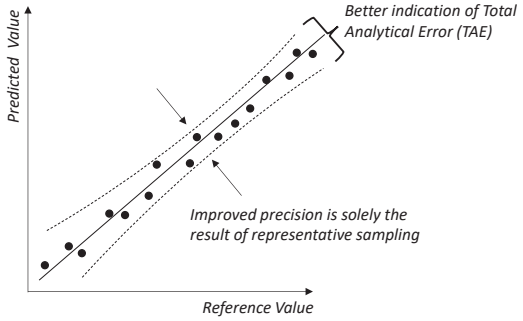

Figure 6: Prediction model generated using representative sampling and optimised spectral data acquisition parameters.

5.3 In-Line PAT Implementation - numerous problematic issues

This example represents a hybrid between at-line and in-line PAT sampling in the pharmaceutical industry. The manufacture of oral solid dose (OSD) formulations for pharmaceutical tablet production always requires a blending step of the powder components used for a specific formulation. In batch processes, this blending is typically performed using a rotating blending system ('V-blender' or IBC type) until a suitable endpoint has been reached. It is problematic that there are still organisations that attempt to sample such a 3-dimensional lot using non-representative insertion thief systems that not only generate biased results but also segregate the local blend through the introduction of a physical device into the powder bed. The use of this kind of device has resulted in endpoint times being set too high and this can result in degradation of the powder blend due to attrition, resulting in changes in particle size distributions and de-mixing phenomena (Muzzio, et al., 2003).

This problem has been somewhat reduced by the introduction of NIR spectrometers that can rotate with the blender and obtain a spectrum for the blend for each rotation. This single measurement represents a sensor grab sampling situation, but a new twist of aggregating a number of spectra, to generate a 'block', has led to implementation of the Moving Block Methods (MBM) approach for real-time detection of blend endpoints (Besseling, et al., 2015).

However, there are a number of optimisation steps that must be performed to generate reliable PAT data in this fashion of which the most important is block size, which must be validated with the aim to become representative of a unit dose prior to industrial implementation.

The major advantage of a PAT in-line NIR method is that there is now no disturbance of the powder bed during sampling. Provided the raw materials used in the blend are of similar particle size distribution, and the blender is not rotated too quickly, it is claimed from driven OEMs that repeatable estimates of blend endpoints can now be obtained. Perhaps ....

But there is still a remaining downside: There is still no way to extract a 1:1 correspondence sample for reference analysis. The European Medicines Agency (EMA) has addressed this situation in its NIR guidance document and terms such methods as "Dynamic PAT Methods"(European Medicines Agency, 2014).

In particular (excerpt from this guidance),

"Because PAT NIRS procedures are specific to the nature of the manufacturing processes (e.g. sampling frequency adapted to process dynamics), it is not appropriate to prescribe exact requirements for such procedures in this guideline.
An example of the use of NIRS in a PAT application is the monitoring of a powder blend for homogeneity. The blend may be monitored in terms of the measurement of the change of the NIR signal (e.g. its standard deviation) over time (also called moving block standard deviation (MBSD)), where this has been shown to be a valid measure of homogeneity."

Notice the improper use of the word 'homogeneity' in the context of the Theory of Sampling (TOS) in chapter six of Multivariate data Analysis: an introduction to multivariate analysis process analytical technology and quality by design (Esbensen and Swarbrick, 2018). But that aside, the guidance clearly states in section 5.1. that representative sampling of a 3-dimensional lot is difficult. But EMA states that this is impossible!

So, how can a quantitative measure of blend potency be made using PAT if proper sampling is impossible? This is where the risk-based approach of PAT must be considered. Figure 7 provides an example of a blend uniformity curve, measured by NIR spectroscopy combined with the Moving Block Standard Deviation (MBSD) measure.

The main assumption is that any point below the Endpoint Detection Limit represents a state of powder uniformity (N.B. not homogeneity!). This blend is now transferred to a compression room where the powder is either gravity fed, or vacuum transferred to the tablet press.

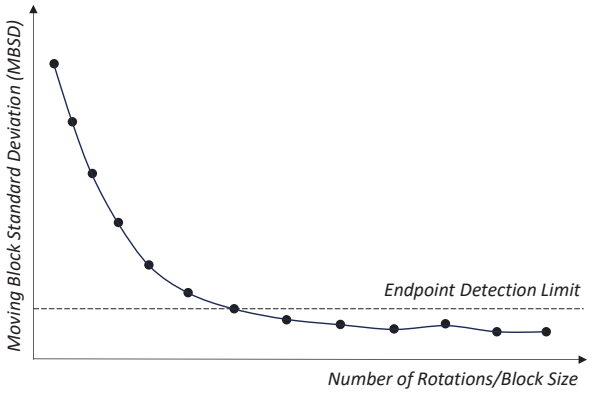

Figure 7: A blend uniformity endpoint curve using the Moving Block Standard Deviation (MSBD) measure.

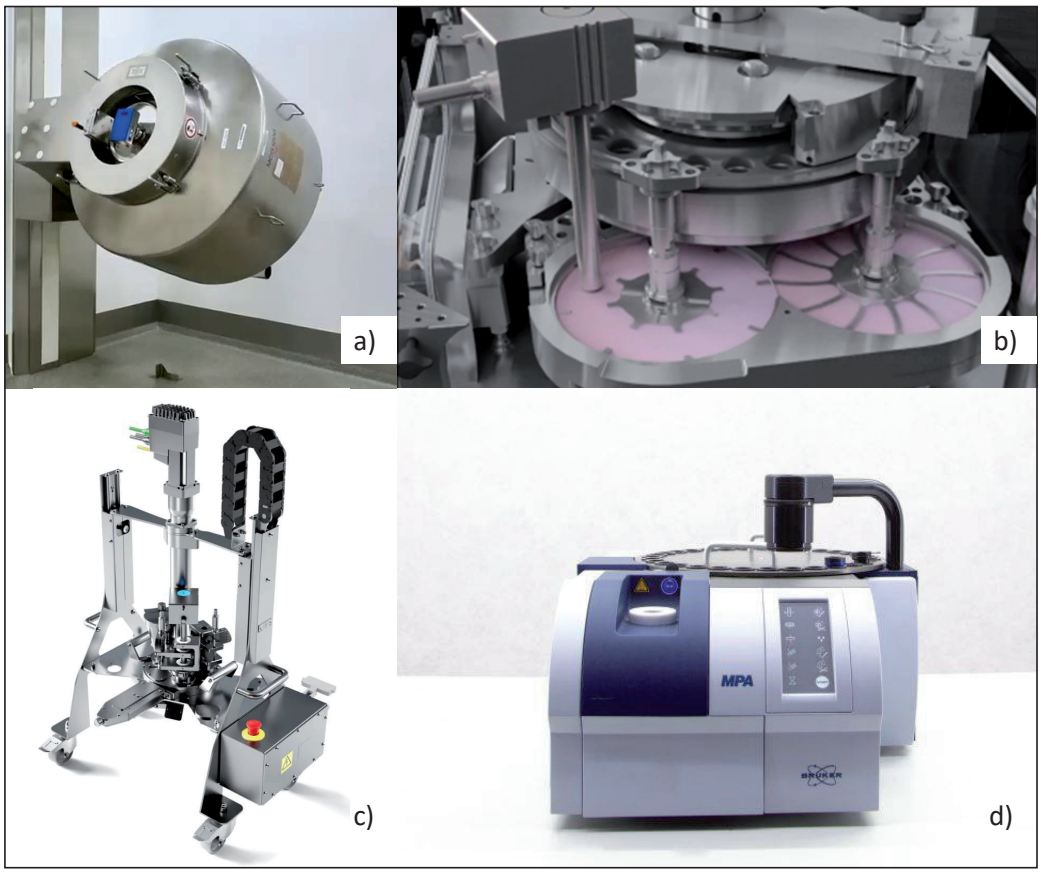

Figure 8: Sampling implementation strategy for assessing powder blend uniformity using PAT, a) NIR system attached to a rotating blender, b) NIR system implemented into a feed frame, c) a feed frame simulation device for calibration development and d) assessing pressed tablets using an at-line NIR spectrometer. *Caveat: examples are meant for illustration of principles only; no identification of company, personnel or equipment brand is intended).*

A tablet press can be considered to be a compacting spinning riffler (Romañach, 2015) and thus, a single tablet may be considered to be a representative sample. There is here a powerful opportunity in measuring a series of tablets and analyse the residual variability using a variogram (Esbensen and Swarbrick, 2018; Danish Standard, 2024). From a variogram can be estimated a Minimum Possible Error (MPE), which represents the minimum remaining total uncertainty due to sampling-and-analysis.

But there is even another approach than measuring discrete tablets - which is to place an in-line PAT NIR analyser into the feed frame of the tablet press. This is the spinning riffler section of the press and it is a bona fide representative sampling system (see e.g., the article by Romañach in this SST issue). To comply with the 1:1 correspondence between PAT measurement and reference analysis aliquot, there are two approaches,

1. A timing sequence can be implemented where a tablet(s) is extracted from the press which corresponds to the time the PAT measurement was made, or,
2. Use of a feed frame simulator (Expo Process Analytics, 2025) to make blends of various concentrations and measure them – 'as is' - in the feed frame using the full-scale on-line PAT device.

The impact of using a grab sampling approach for measuring powder characteristics in hoppers or chutes prior to tablet compression and analysing these samples using a reference method leads to the same adverse calibration model results as was shown in Figure 5 for the at-line case, whereas, using a feed frame simulator, or analysing 'timed' discrete tablets against the feed frame results in resolved calibration situations as depicted in Figure 6.

Figure 8 presents a potpourri of equipment and approaches for the entire process of calibration development using PAT for powder uniformity and quantitation. Caveat: examples are meant for illustration of principles only; no identification of company, personnel or equipment brand is intended).

The final implementation can be used as a PAT approach for two-fold assessment of blend and content uniformity of pharmaceutical powder blends, and can be summarised as follows,

1. Use the results of in-line NIR for endpoint detection of powder blending.
2. Develop a representative calibration on powder blends covering the specified analytical range using either a feed frame simulator or by implementing a PAT sensor directly into the full-scale feed frame and collecting compressed tablets for reference analysis.
3. Develop an at-line method based on tablets generated from production batches (and from batches made on the feed frame simulator as a back-up method).
4. Run the feed frame NIR during production to look for process trends and deviations.
5. Compare the batch process feed frame trends to the NIR blend uniformity data for joint assessment of blend uniformity and content uniformity.

6. Conclusions and Future Perspectives

It does not matter if a PAT approach is at-line, in-line or on-line, the principles of proper sampling and validation must be complied with in all cases. PAT analysers must be implemented and validated in the same way as any other analytical method, the main difference if that a PAT instrument is designed to measure continuously outside of a laboratory.

This requires that the PAT instrument is robust to its surroundings (see e.g., the article in this SST issue by Dusko Kadijevic) and must be positioned and implemented to be able to characterise a sample volume that is representative of the current state of the process – this can only be accomplished by a proper process sampling interface (Esbensen in this issue). Therefore, most of the development work behind chemometric PAT calibrations is often focused on acquiring a representative sample. There is absolutely nothing special about PAT in this regard.

The extraction of an analytical aliquot for sensor assessment has been the topic of endless debate and innumerable articles within the realm of PAT, but only a very few are based on full understanding of the three-domain complexities involved (sampling / analysis / data modelling), ibid.

The economically dominating pharmaceutical blend uniformity problem raises several issues that are also documented in foundational NIR method guidance documents. In particular, the extraction of aliquots using sample thieves results in the extraction of specimens with no certain provenance; and they disturb the uniformity of the entire 3-dimensional lot through induced segregation.

The blend uniformity problem requires some thinking outside the box and mandates correct usage of guidance documents to devise a risk-based strategy to achieve the critical objectives of assessing blend uniformity and content uniformity. A solution based on commercially available systems was indicated here, a solution that goes a long way to minimise sampling errors and focus the PAT measurements on the chemistry/biology of the samples being measured.

Future sampling systems must be designed where the exact aliquot measured can indeed be extracted from the sampling device without committing Incorrect Sampling Errors (ISE) (TOS) to improve the 1:1 sample to PAT correspondence. This will avoid situations where newcomers will be less tempted to use wrong preprocessing methods or revert to automated modelling scenarios based on AI that not only over-complicate the calibration development but are in reality black box in nature, are rarely interpretable, and cannot be properly validated. All these concerns will first be eliminated if/when a perfect process sampling interface is introduced – OEMs take notice!

Reliable PAT chemometric model development starts with selection of the optimal sensor technology for acquiring the most relevant multivariate sample spectra that are guaranteed representative of the contemporaneous process stream segments (see Esbensen in this issue) - and finishes with reliable prediction of analytical results, generated by properly calibrated and validated chemometric prediction models (Martens and Næs, 1991; Wold, 1995; Massert et al., 1997; Adams, 2004; Esbensen and Geladi, 2010; Esbensen and Swarbrick, 2018; Höskuldsson, 2024).

There is no short cut to the competences needed. The analytical domain notwithstanding, chemometricians have a lot to teach samplers about the power of multivariate spectra, but the opposite relationship: proper sampling before analysis, before data analysis is even more important. We are all in this together!

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A Manual Process Sampling Solution for In-Service PAT Inspection of Wind Turbine Blade Bearing Lubricants

By Hans S. Møller[1] and Kim H. Esbensen[2]

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ABSTRACT

Wind turbine failure is causing debilitating equipment/operational downtime and is always very costly due to the exceptional efforts required for repair or replacement – especially so for offshore turbines. Condition based monitoring (CBM) of grease lubricated turbine components (main and blade bearings) can greatly improve turbine reliability and reduce costs when properly applied. In-service monitoring of grease lubricated bearings is a win-win benefit at all levels. But is it possible to apply a PAT approach for in-service grease monitoring to develop a reliable warning system before breakdown? Alas, not directly - it turns out that certain necessary modifications to the standard PAT concept are needed. Here we present the development history of a manual process sampling solution for in-service PAT inspection and monitoring of grease lubricated main components in wind turbines.

1. Introduction

By demand for continuous operation 24/7/365, wind turbines can only operate with the necessary reliability if serviced by targeted condition monitoring of grease lubricated main components. This stringent demand is critically dependent upon reliable monitoring of the state of the grease in the bearings involved. Wind turbine grease lubricated bearings therefore need reliable monitoring, which must be as logistically easy as possible. For onshore wind turbines this is a fairly easy practical task (easy access), while for marine installations, offshore wind farms, this constitutes a significantly bigger logistical and engineering challenge (accessibility, weather, safety).

The task of inspection and monitoring both on-and offshore wind turbine grease lubricated bearings can be viewed under the general scope of Process Analytical Technology (PAT). Monitoring of a manufactoring/processing compositional component, or an active structural process component over time is usually a comparatively easy task provided there exists a relevant ´PAT sensor´able to interact with (in the present case) the in-situ grease located between the rollers and raceways of blade and main bearings in real time.

Preferentially a sensor yielding a multivariate spectral signal, which would allow a ´classic' spectroscopic PAT approach, calibrated and validated with chemometric models (Esbensen and Mortensen, 2010). Developing such a sensor would be truly revolutionary for the tribotechnology sector and its desire to offer the best, most efficient in-situ monitoring approaches.

Alas … this has not been possible because of the overpowering practical difficulties involved in extracting either a spectral signal, or a physical sample from in-service grease lubricated bearings, far less a documentable representative signal/sample (sensu TOS).

The purpose of the present process sampling of in-service grease is to facilitate condition monitoring of the targeted bearings. The primary marker for any bearing's condition is the number, size, and morphology of wear debris in the active grease.

For these reasons the tribotech sector has for 15 years been involved in developing a manual alternative but with all the desirable benefits of PAT monitoring intact.

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The present authors have reported from this challenging journey at three LUBMAT conferences (Møller et al., 2012; Møller et al., 2014; Møller et al., 2016). Here we describe the objectives for this technological journey and summarise key findings and results. Our specific viewpoint is to develop an alternative manual process sampling solution for in-situ PAT inspection and monitoring of wind turbine grease lubricated bearings. The main thrust of the present article is to explain how, confronted with insurmountable obstacles for standard PAT, it has never-the-less been possible to find creative alternative engineering manual approaches obtaining the same solution benefits.

2. Summary of leading up history

This article presents the challenges and achievements over a period of 10+ years of developing an approach for representative sampling of grease from blade bearings based on the principles of the Theory of Sampling (TOS) (which is not necessarily a feature in current 'solutions') for condition assessment of blade bearings based on advanced grease analysis. Below, we focus on manual PAT monitoring of blade bearings. But first a brief introduction is provided of the main components of a modern offshore wind turbine.

An offshore wind turbine consists of the following main components, as shown in Fig. 1:

1. rotor blade assembly (hub and three blades)
2. nacelle
3. tower
4. transition piece

The rotor blade assembly comprises three blades, each with a bearing at its root. Blade bearings serve two purposes: i) connecting the blades (the unit that captures energy from the wind) to the nacelle; ii) enabling the blade to rotate around its longitudinal axis, i.e. to change its pitch (defining the wind attack angle with respect to the blade surface). For this reason, blade bearings are often alternatively termed 'pitch bearings', Fig. 2.

Since pitch bearings, by their nature, do not rotate continuously but only oscillate through a few degrees, conventional PAT-related monitoring methods such as vibration monitoring are not applicable. Therefore, the method described below is currently the best and most well-documented method for condition monitoring of blade bearings.

When a blade bearing has been assembled at a construction site, it is no longer possible to access its active part, i.e., the space between the outer and inner races to extract grease samples. However, in operation there is a continuous supply of new grease to the bearing, while the excess grease is pressed out and collected in containers located on either the outer or inner race of the blade bearing. These containers are accessible for extracting in-service samples, Fig. 3.

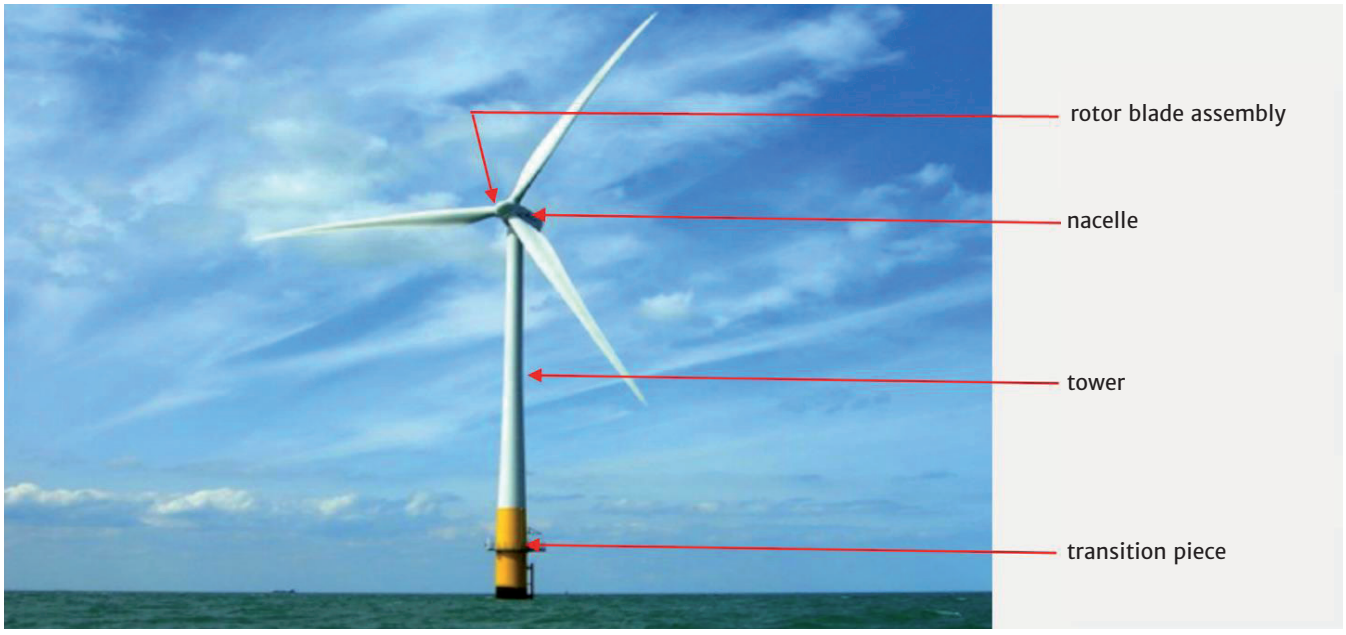


Figure 1: Main structural components of an offshore wind turbine.

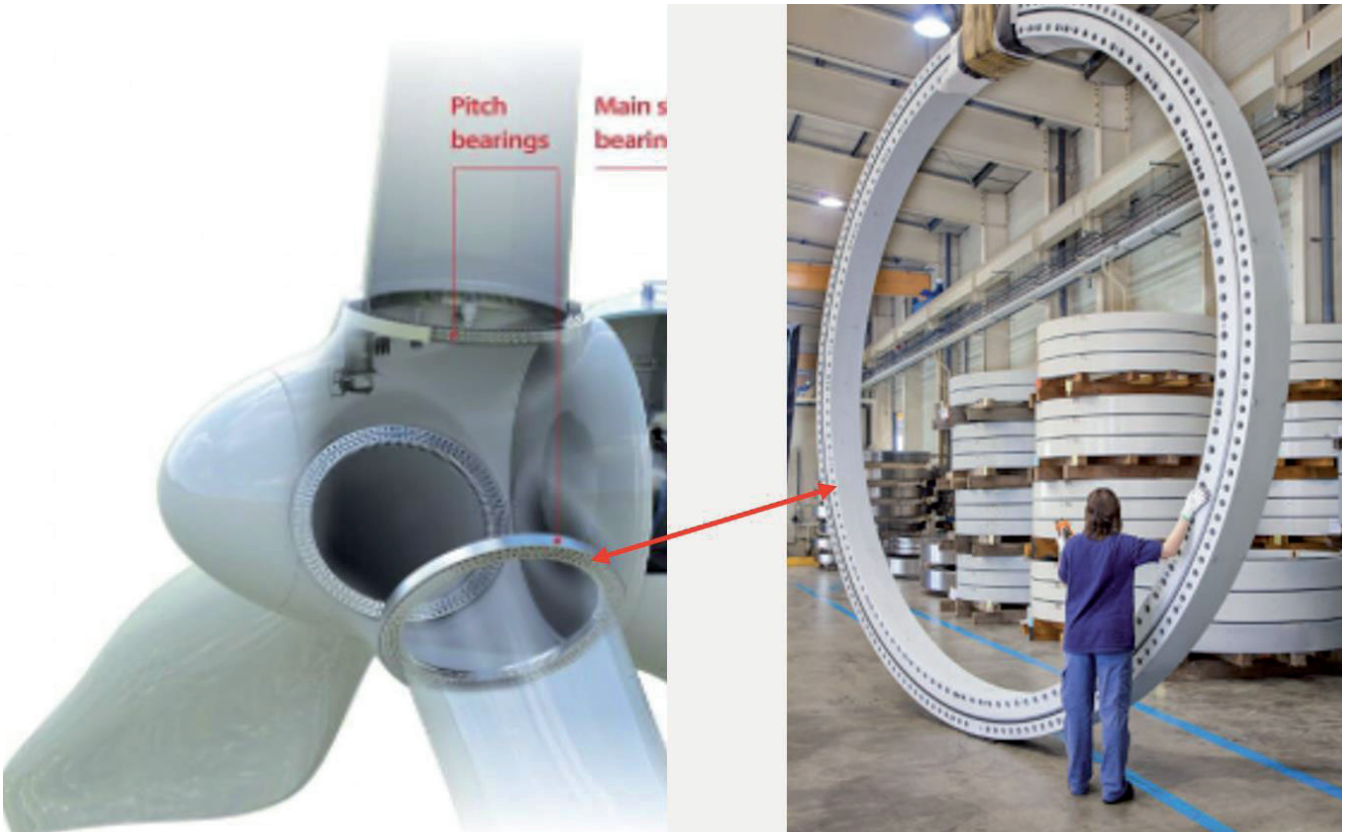


Figure 2: Rotor blade assembly (left) and a blade (=pitch) bearing (right). Note the raceway between the outer and inner races, from where samples of the active grease shall be extracted.

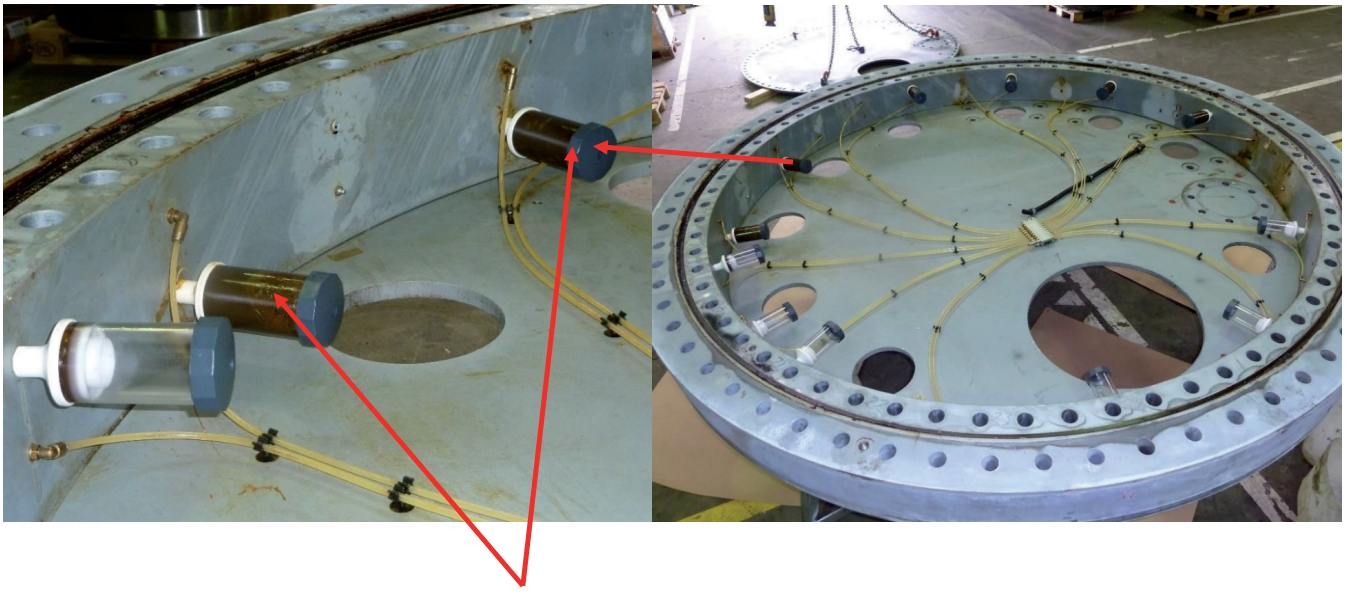


Figure 3: Blade bearing in a 3.6 MW turbine with grease collecting devices ("Grease cups") fitted to the inner ring. These grease cups are accessible for sampling of in-service grease samples used for condition monitoring, see Figure 5.

For calibration of the present new sampling approach, it was possible to carry out a comprehensive 3-D heterogeneity characterization of the grease in the 360 deg active zone of blade bearings; this was reported in an earlier study (Møller et al., 2016). A summary will suffice for the present purpose.

With a bearing dismantled for onshore inspection, it was possible to conduct sampling of the active raceway in a representative fashion in full compliance with TOS, as illustrated in Fig. 4. Dismantling allows sampling and full characterization of the variation and properties of the grease along the full 360-degree active zone of the bearing in the space between the raceways. This sampling scheme, here termed the 3-D heterogeneity characterization, forms the reference against which the in-service grease cup sampling can be compared and evaluated.

From a TOS point of view, the in-service grease cup sampling, and analysis (performed in the analytical laboratory) is fit-for-purpose representative (Esbensen and Mortensen, 2010); therefore, it is the best available proxy for direct characterization of the properties of the active raceway grease - be this in the form of an average over the full circumference, or as a mapping of the peripheral compositional variation in the active zone between the raceways (Møller et al., 2016).

The analytes used in the reference characterization were i) content of ferro-magnetic iron, ii) water content, and iii) particle size distribution of wear debris.

In total 175 grease samples were included in this comprehensive reference study.

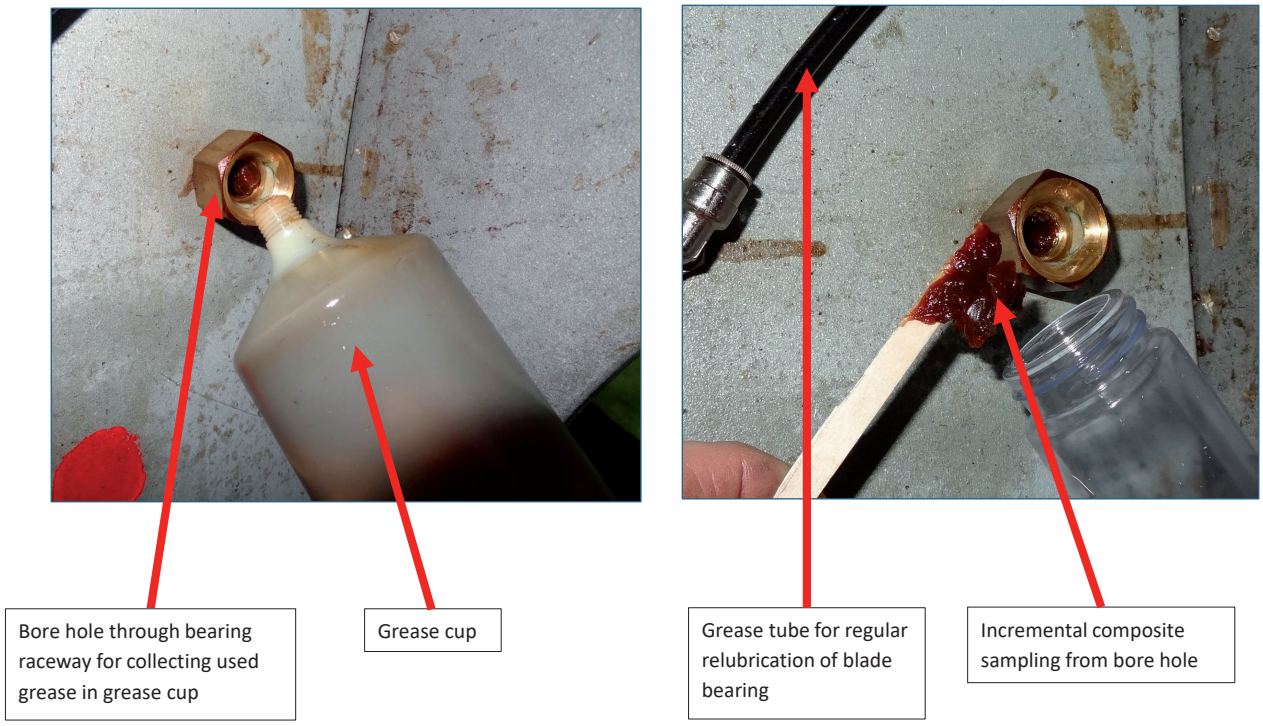
2.1 In-service, in-situ condition monitoring

Blade bearings have an atypical mode of operation, as they do not normally rotate when the turbine is in operation. This means that traditional, highly successful vibration analysis is not an option. Physical sampling (and analysis) of grease from the active blade bearings is therefore the only useful method for obtaining reliable data for assessment of current operating conditions. The most important analytes for this purpose is the content of wear particles, their size distribution and their morphology. Dedicated laboratory procedures have been developed, which have proven to be suitable for this purpose. It is the experience that only wear particles larger than ~100 µm are relevant for a condition check of blade bearings (Møller et al., 2012, Møller et al., 2014, Møller et al., 2016).

2.2 Grease cup samples - a match to PAT process samples

As a rule, during inspection visits to active offshore windmill nacelles, which takes place for other monitoring purposes as well, grease extraction is also routinely performed from two randomly selected grease cups along the complete inner raceway of a given bearing, Figs. 3,5. These samples form bona fide PAT samples extracted from the process.

Figure 4: Representative reference grease sampling from a dismantled 3.6 MW blade bearing. Increments from every second ball support hole were used for 3-D heterogeneity characterization of the grease in the complete 360 degree active zone in the space between the raceways. This is a 1-to-1 match analogue to "stopped belt" sampling in conventional PAT.



Credit: Photos by Mr. Ole Grosser; used with permission.

Figure 5: Manual PAT at work in the Baltic Sea. Inspection and monitoring crew visiting the nacelle of windmill Rødby 2, Baltic Sea is extracting composite samples from grease cups holding used blade bearing grease (see also Fig. 3).

We refer to (Møller et al., 2016) for technical description of three case histories documenting the calibrating comparison between the reference and the present grease cup sampling. Here it was demonstrated how this approach can accurately determine the physical condition of the targeted bearings. These comprehensive results led to the conclusion that 'grease cup' sampling is a satisfactory proxy for representative sampling from an active raceway.

3. Discussion

Based on the Theory of Sampling (TOS), it has been possible to develop an alternative method for acquiring representative samples of active grease from blade bearings in offshore wind turbines. This is a crucial prerequisite for development of a practical, economically reasonable and logistically operational condition monitoring approach of in-service blade bearings. The new method has been compared and evaluated to a comprehensive, fully TOS-compliant refence sampling performed on dismantled bearings; this reference sampling is a direct analogue to 'stopped belt' reference sampling in the conventional PAT context, allowing realistic calibration and evaluation.

4. Conclusions

It has been possible to develop a fully validated manual process sampling solution for PAT in-situ inspection of wind turbine bearing grease. This is the only possible approach for Condition Monitoring of in-operation wind turbines.

5. Perspective

Globally, in many countries, offshore wind turbines are becoming an increasing part of the technical backbone for the necessary transition to a CO2- free renewable energy supply. Offshore wind turbines are extremely capital-intensive investments, for which reason cost-effective methods for operating and monitoring these assets are highly desirable. To solve this task, many different analytical tools (physical, chemical, AI) are used today to process today's readily available on-line data remotely onshore (with obvious needs for automation).

However, there are still main components, for which no documented method for continuous operational monitoring exists – yet. To monitor the state of the crucial blade bearing components, the authors consider regular in-service physical PAT sampling and analysis of bearing grease to be the most suitable method available today.

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Giants of Sampling 4: Robert Hallowell Richards

By Alan F. Rawle[1]

DOI: 10.62178/sst.004.010

1. Introduction

Robert Hallowell Richards was an early but crucial contributor to the theory of sampling. There are several interesting points associated with him:

- He lived to be over 100 years old, born in 1844 (August 26), he died in 1945 (March 27).
- He was in the very first group of students at MIT (Massachusetts Institute of Technology) when it opened in 1865 and graduated in 1868. He then spent 46 years working at MIT before retirement in 1914.
- His first wife, Ellen Swallow Richards, has had much more written about her than her husband as she (among other things) coined the term ecology (although spelled she first spelled it 'oekology'). She was the first female instructor at MIT in 1873 and had published far more extensively than Robert (See: https://en.wikipedia.org/wiki/Ellen_Swallow_Richards).

With regard to sampling, Richards inadvertently re-wrote the laws of physics for convenience, and we'll explore that point later.

In terms of source material, Robert Richards wrote an autobiography (Robert Hallowell Richerds His Mark (Boston Little, Brown and Company 1936) Original cost $3). In contrast, Ellen Swallow Richards has had at least 5 biographies and similar books written about her. Richards' autobiography is written in more of a story-like, rather than scientific, manner and may reflect the fact that Richards was 92 or so years old when the book was published.

In the Technology Review (an MIT publication), Arthur Winslow (a graduate of 1881) wrote, in July 1908, an article commemorating 40 years of Richards' service with MIT, so we have plenty of source material to use.

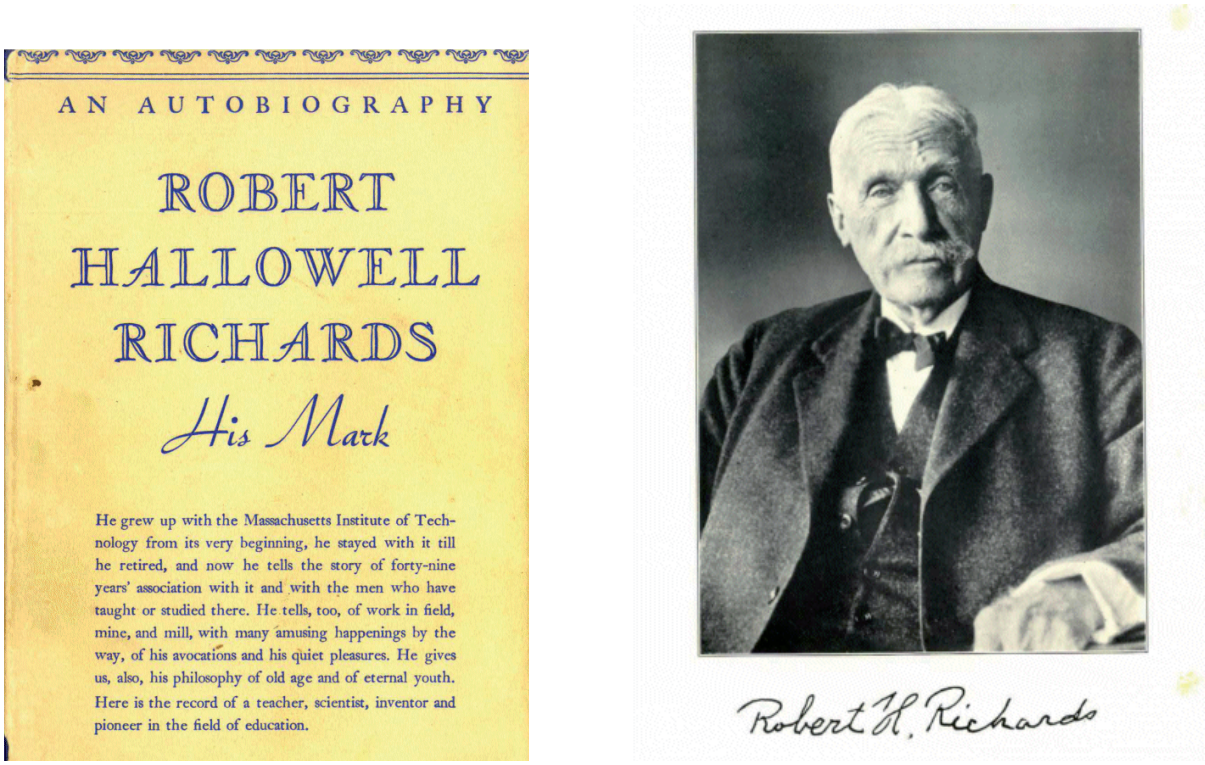

Figure 1: Dust jacket of Richards' autobiography together with the inset picture.

1 Retired. Hardwick, Massachusetts, USA.

Figure 2: Birthplace of Robert Hallowell Richards: Oaklands, Gardiner, Maine as it was in 1852 or so (woodcut from J W Hanson History of Gardiner, Pittston, and West Gardiner Published William Palmer 1852).

2. Early life and education

Robert Hallowell Richards came from a privileged background. 2 towns in Maine were named after his ancestors – Gardiner, Maine (where he was eventually buried) was named after his great-great grandfather, Dy Sylvester Gardiner, and Hallowell (from which his middle name originated) was named after great-great grandfather, Benjamin Hallowell.

The family owned a large estate called "Oaklands" on the Kennebec River. Maine and it was here that Robert was born on August 26, 1844 the sixth child of Anne and Francis Richards.

He was sent to school in England (in 1857 at age 13) with his brother, Harry ("Richards Major and Richards Minor") thanks to his father's interest in the country and lived at Cadlington, Horndean (home of Sir Michael Seymour) for one year before moving to Moorland Cottage, Purbrook, Hampshire (and hearing his first nightingale sing there).

His 4th and 5th years in England were spent at Wellington College, Berkshire where he was influenced by a Mr. Daykyns ("made me study"). Richards states "Mr. Daykyns was also very fond of nature. I once threw a stone at a bunch of sparrows and chaffinches that sat on a hedge. I laughed at my prowess, but he reprimanded me, saying it was wrong to mistreat birds. To this day I have not forgotten the change that was wrought in me by that simple remark".

Figure 3: Oaklands today HABS 1962 (Public Domain Wikipedia)

He returned to the US in 1862 (aged 18) where he moved with his mother to Boston. He tried to get into Harvard aged 19 and failed while his brother, Harry, was very successful there. He then attended Phillips Exeter Academy where, apparently, he was a complete misfit. He states, "I could not adapt myself to the method of education which revolved around learning dead languages by heart". These 'dead' languages were Latin and Greek.

He also tells a story about a mathematics teacher there (called 'Bull' Wentworth) where the conversation went:

"Well, Richards, where did the Pilgrims land?"

"I, having just returned from five years in England, did not know there were such things as Pilgrims". I replied solemnly "On the shore, sir"

In February 1865, his mother sent him a letter informing him that a connection and friend, Professor William Barton Rogers, was just starting the Massachusetts Institute of Technology (MIT) Boston, and she thought that this school might satisfy his needs better than Harvard. She was correct in that opinion and Robert thrived from the practical "observe, study, and record" manner of education. He learned the usefulness of the German language as his textbook on ore dressing was written in that language (Peter Ritter von Rittinger's Lehrbuch der Aufbereitungskunde?). Richards remarks "The method of teaching was completely new to all of us.

We found ourselves bidding goodbye to the old learn-by-heart method and beginning to study by observing the facts and laws of nature" and "We learned... how to observe, how to record, how to collate, and how to conclude". He states in his autobiography "Education ceased to be a plague spot and became a delight".

After graduation in 1868, Richards was asked to continue at MIT as an instructor and thus began 46 years of service. "In 1870, Professor Rogers suffered a stroke. Professor Runkle was elected to succeed him. Storer, the best professor of chemistry the school ever had, was so bitterly opposed to this move that he put on his overcoat and walked out of the school, never to cross its threshold again". "I, being the senior young man in his department, found myself acting head of chemistry of four months in the spring of '71, not be appointment, but by circumstances. It was a case of the old adage: "Nature abhors a vacuum"".

1871 – 3 years after graduating Richards found himself in charge of a department of mining engineering... He continued in that department until retirement in 1914.

He documents his time as follows:

- 1871 – 1873 Mineralogy, assaying, mining laboratory, metallurgical laboratory
- 1873 – 1878 Mineralogy, mining engineering, mining laboratory, metallurgical laboratory
- 1878 – 1883 mining engineering, mining laboratory, metallurgical laboratory, Secretary of the Faculty
- 1883 – 1889 mining engineering, metallurgy and the two laboratories
- 1889 – 1901 mining, and non-ferrous metallurgy, and the two laboratories
- 1901 – 1914 ore-dressing and the two laboratories

He determined the settling/sedimentation curves of materials settling under gravity in water, thereby establishing the fundamental principles of sorting ore by means of jigs and other machines. Indeed, in the days that I took an Extraction Metallurgy course at university we used his classic galena and quartz system as an example of mixed density settling and separation. This is the hindered settling principle where in free settling, a quartz particle (s.g. 2.6) 3.5 times the diameter of a galena particle (s.g. 7.6) settles at the same rate. Under hindered settling conditions (e.g. in a medium of higher density or concentration) the particle of quarts can be 7 times the diameter of the galena particle to settle at the same rate. This has great implications in the concentration and separation of ores and is the basis of the hydraulic classifier. During the period 1895 and 1900 Richards developed the so-called Richards Pulsator Classifier and Pulsator Jig for size and separation of minerals from gangue. The pulsator principle of upward-rising water currents a jig bed can be active 100% of the time a doubling in improvement over the earlier Harz jig. Richards also studied boat paints by running boats though water to see what friction was generated. From these tests he developed a graphite-based paint with the friction about ¾'s of that of comparable paints. He had a wide range of interests including nature (which included hunting and fishing), astronomy, photography, and glassblowing. He was very much an expert in the latter and demonstrated this in several of his metallurgical classes.

Earlier, in 1869 Richards had developed a filter pump for laboratory use which led to later improvements in the form of a jet pump using the injector principle.

Richards served as president of the American Institute of Mining Engineers (AIME) in 1886. He published around 35 original papers in the Transactions of AIME. In 1915, Richards was presented with a gold medal from the Mining and Metallurgical Society of America. The award was under the topic of "Advancement in the Art of Ore Dressing".

Richards main claim to fame, other than being a graduate of the first year of MIT in 1858, was his 4 substantial volumes entitled 'Ore Dressing' (5 volumes if you include the separate index) published initially in 1908 or 1909. Later editions attempted to condense these into 2 or 1 volume as was the forerunner (2 volume set) edition published by The Engineering and Mining Journal in 1903.

He did not take royalties on these publications to reduce costs for his students. These have been developed into print on demand and Google Books downloads, but I still retain an original full set plus the index. The pertinent volume dealing with sampling issues is Volume 2. The page numbering and sections are somewhat confused (IMHO) and thus care needs to be taken in looking through the different volumes from the different years and compilations.

Richards begins his introduction to sampling with the sentence "Sampling consists in obtaining, from a lot of ore, a small portion to weigh out for assay, which shall represent as perfectly as possible the exact proportions of the constituents in the original batch of ore". He then runs through standard manual (e.g., cheese scoop sampler, shoveling) and automated methods (Vezin, Snyder, Collom, Brunton) before proving a table of minimum masses linked to top end size of the sample. I have used this table many times.

Let us examine how the calculation was made. Richards explains the calculation thus: "First, to decide what weight (w) should be taken for assay or analysis after the ore has been ground to 100-mesh (approximately 0.125 mm. diameter) ; second, to compute the number (n) of maximum sized grains passing through a 100-mesh screen that would weigh (w); and third, to cut down to a weight after each crushing which will be equal to n of the maximum sized particles".

My first clue was that the sample size for a top end of 1mm (1000 microns) was stated to be ~ 1.5 kg.

Early in the 1990's I'd carried out similar calculations used in an old Malvern Instruments' application note. I'd come up with a minimum mass of ~ 1.36 kg based on a density of 2.6 g/cm^3 (approximation to silica) which is in the same ballpark. The basis for my calculation was a standard error of 1% (SE is proportional to $n^{1/2}$ so a 1% SE requires 10000 particles) based on the 99th percentile of the distribution. This requires 10000 particles in the x_{99}+ part of the distribution (which makes up 1% of the total mass so we need to multiply by 100 (98 is the actual correct factor as shown by Gy), so we can calculate a theoretical minimum mass for a 1mm top end as (with the size in mm converted to cm):

$$M_s = 10000*100*(\pi/6)*(1000*10^{-4})^3 *2.6$$
$$= 1361 \text{ g} \sim 1.36 \text{ kg}$$

It is the easy to spreadsheet the calculations to allow a simple comparison with the stated table and those numbers supposedly given by Vezin in the Richards' table.

We note that the comparison is excellent and could be made identical by a change in assumed density from 2.60 g/cm^3 to 2.86 g/cm^3.

After giving us this important table, Richards then states" The above rule demands finer crushing than practice indicates to be necessary, and it is, therefore, more expensive than is wise". He further states referencing Brunton "Brunton's results, however, show quantities that are largely in excess of practice".

Table 1: Minimum masses of sample required according to Richards (1903/1908)

This rule may be said to use a constant number of particles whatever their size. The following figures show the weights of different sizes required by this rule on the basis of 0.1 assay ton (2.917 grams) of ore through a 100-mesh screen (0.125 mm.) :

128	mm.		3,131	metric tons.
64	"		391	" "
32	"		48.9	" "
16	"		6.12	" "
8	"		764.6	kilos.
4	"		95.57	"
2	"		11.95	"
1	"		1.493	"
0.5	"		186.7	grams.
0.25	"		23.33	"
0.125	"		2.917	"

Table 2: Comparison of the Richards' table with calculations based on a standard error of 1% on the x99 (assumed spherical particles).

d (µm)	d/10000	d^3	Density (g/cm³)	10000*100*(π/6)	Minimum Mass (g)	Vezin (1865/1866)	Vezin/Rawle
1	0,0001	1E-12	2,6	523598,7756	0,000001		
10	0,001	1E-09	2,6	523598,7756	0,001361		
100	0,01	0,000001	2,6	523598,7756	1,36		
125	0,0125	1,9531E-06	2,6	523598,7756	2,66	2,92	1,10
200	0,02	0,000008	2,6	523598,7756	10,89		
250	0,025	1,5625E-05	2,6	523598,7756	21,27	23,3	1,10
500	0,05	0,000125	2,6	523598,7756	170,2	186,7	1,10
1000	0,1	0,001	2,6	523598,7756	1361,4	1493	1,10
1500	0,15	0,003375	2,6	523598,7756	4595		
2000	0,2	0,008	2,6	523598,7756	10891	11950	1,10
4000	0,4	0,064	2,6	523598,7756	87127	95570	1,10
5000	0,5	0,125	2,6	523598,7756	170170		
8000	0,8	0,512	2,6	523598,7756	697015	764600	1,10
10000	1	1	2,6	523598,7756	1361357		

Richards work-around is to take a mass based on the square of the largest particles diameter: "By adopting the rule that the weight shall be proportional to the square of the diameter of the largest particles, we shall obtain a set of figures that will in all probability meet the approval of practising engineers; and which have a definite basis, and thereby do away with a great deal of guess work". He then provides a table (his table 369) and graphical plot based on this assumption.

Table 3: Richards ' Table 369 on sampling weights

TABLE 369.—WEIGHTS TO BE TAKEN IN SAMPLING ORE.

Weight.		Diameters of Largest Particle.					
Grams.	Pounds.	Very Low Grade or very Uniform Ores.	Low Grade or Uniform Ores.	Medium Ores.		Rich or "Spotted" Ores.	Very Rich or Excessively "Spotted" Ores.
		Mm.	Mm.	Mm.	Mm.	Mm.	Mm.
.....	20,000	207	114	76.2	50.8	31.6	5.4
.....	10,000	147	80.3	53.9	35.9	22.4	3.8
.....	5,000	104	56.8	38.1	25.4	15.8	2.7
.....	2,000	65.6	35.9	24.1	16.1	10.0	1.7
.....	1,000	46.4	25.4	17.0	11.4	7.1	1.2
.....	500	32.8	18.0	12.0	8.0	5.0	0.85
.....	200	20.7	11.4	7.6	5.1	3.2	0.54
.....	100	14.7	8.0	5.4	3.6	2.2	0.38
.....	50	10.4	5.7	3.8	2.5	1.6	0.27
.....	20	6.6	3.6	2.4	1.6	1.0	0.17
.....	10	4.6	2.5	1.7	1.1	0.71	0.12
.....	5	3.3	1.8	1.2	0.80	0.50	.....
.....	2	2.1	1.1	0.76	0.51	0.32	.....
.....	1	1.5	0.80	0.54	0.36	0.22	.....
.....	0.5	1.0	0.57	0.38	0.25	0.16	.....
90	0.2	0.66	0.36	0.24	0.16	0.10	.....
45	0.1	0.46	0.25	0.17	0.11	.....	.....
22.5	0.05	0.33	0.18	0.12	.....	.....	.....
9	0.02	0.21	0.11	.....	.....	.....	.....
4.5	0.01	0.15	.....	.....	.....	.....	.....
2.25	0.005	0.10	.....	.....	.....	.....	.....

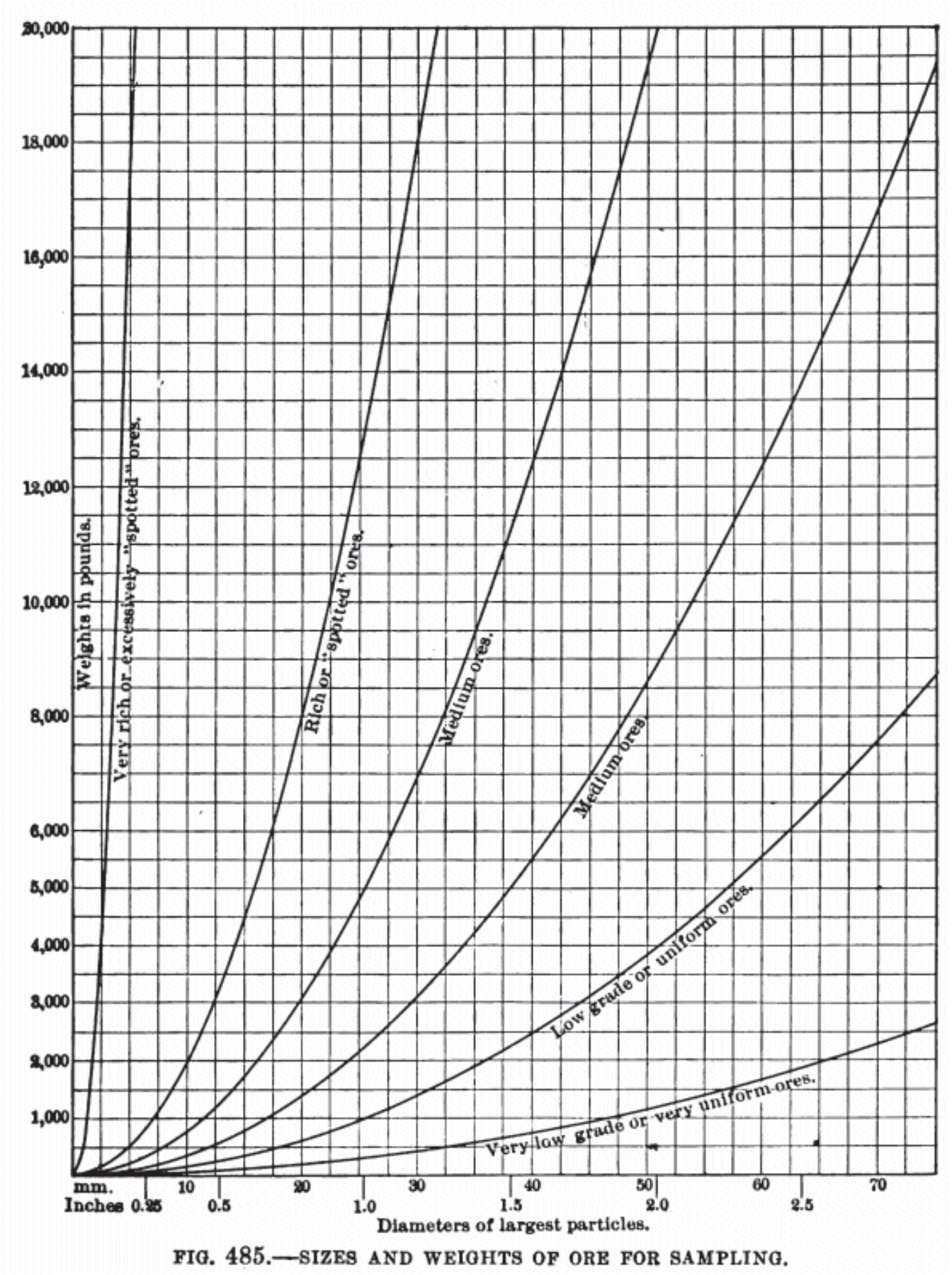

Figure 4: Richards' graphical representation of sizes and weights of ore for sampling

Again, we see the focus on the type of ore to be sampled, and these assumptions have bedeviled sampling theory since the early days. We also note that the basis for these calculations is usually the derivation of the fundamental sampling error (FSE) ignoring the fact that this is usually the error (or variable) amenable to calculation and only 1 of 7 or 8 other errors which are often considerably larger than this.

The pertinent rules for how much (mass) of sample to take for it to be representative of the whole are based on how many particles are present in the top size (band) to be considered together with the desired precision (expressed as the standard error in statistics). These larger particles may be few in number but make up a substantial portion of the mass or volume of the total system in comparison to the finer or dust-like particles that may be present in the millions or billions. However, we do note that, in many ore dressing scenarios, the material of interest may be softer, denser and thus present in the finer/finest fractions than the unwanted gangue material (typically harder and less dense, if quartz or aluminosilicate).

It is worth exploring in some detail this $M_s \sim fD^a$ formula (where f is a form (shape) factor - 1 for cubes and $\pi/6$ or ~ 0.524 for spheres) multiplied by the density of the material – converts volume to mass - and a is a constant (exactly 3 in theory). Richards had 'amended' this to $M_s \sim fD^2$ on the basis of engineering convenience perhaps indicating the essential differences between a physicist/chemist (exact) and an engineer (empiricism). Thus, I find in my university extraction metallurgy notes from the late 1970's "the minimum mass requirement of "$M_s = kD^n$ where n = 2 to 3, theoretically 3...". This is perhaps an area where the old saying applies "In theory, theory and practice agree. In practice they do not".

Going back to 1922, not long after the publication of Richards' Ore Dressing tomes, we have Demond and Halferdahl in their 2 papers ("Mechanical sampling of ore" Engineering and Mining Journal-Press, v. 114, no. 7, p. 280-284 & "Sampling spotty gold ores" Engineering and Mining Journal-Press, v. 114, no. 22, p. 948) on the mechanical sampling of ore working on the expression:

$$W = kD^a$$

where W is the weight of ore, D is the diameter of the largest particle, and k and a are constants. They tabled sampling data for several crushing plants, where a, the exponent to which the diameter is raised, ranged from 1.0 to 3.76.

They claimed that an a as low as 1.4 should never be used and that a should never be as great as 3.0. Again, we see the difference between scientific exactness and an empirical or convenient approach. This 'convenience' lasted from Richards' time to the 1950s' when Pierre Gy got us back to the correct theoretical approach.

Richards mentions Brunton in his ore dressing books but not in his autobiography, so we don't know if they actually met. We assume that they did. Richards certainly had met Vezin and quotes: "Henry A Vezin was an old friend of mine for many years. In the early days, he knew more about ore-dressing, as practised in Germany, than almost anyone in that country. He was educated there. He was always visionary, however. My first introduction to him was in 1872, riding over the Rocky Mountains in Colorado with two men. We came to a place called Montezuma, where we were treated badly. Vezin told us was that there was one man with us who had written bad things about the place" and continues ""Vezin was a mining expert, mainly a specialist in concentrating. I last met him in Denver, not long before he died, and had a very funny interview with him. It was very characteristic of the man. He was so overjoyed at seeing me that he could hardly contain himself, and he began to tell me a story, and that reminded him of another; he began to tell me that one, and it reminded him of still another and so on. When I left, I concluded that he must have started about fifteen stories and not finished one".

On June 4, 1875, Robert (Bob) Hallowell Richards married Ellen Swallow. The 'courtship' had lasted 2 years or so and seemed to be an intellectual match. In his autobiography Richards wrote, "I had no ideas of what a wife ought to be to me, or what I ought to be to a wife, but I knew that Ellen Swallow's aims in life were along the lines which mine had seemed to follow. I admired her pioneer spirit, and I think she respected me for the hard work which I was doing. The inevitable happened, and one day in the laboratory (June 6th, 1873) shortly after she had received her B.S., I asked her to become my wife. She wished to think it over for a little, and to my everlasting joy, she decided to accept my offer". He was 3 years younger than she was.

Ellen (or Nellie as she was known) has had far more books published about her than many other women. She published extensively and we could write 5 or 10 times more about her than her less famous husband. I would recommend the book by Pamela Curtis Swallow entitled 'The remarkable life and career of Ellen Swallow Richards' (Wiley TMS 2014).

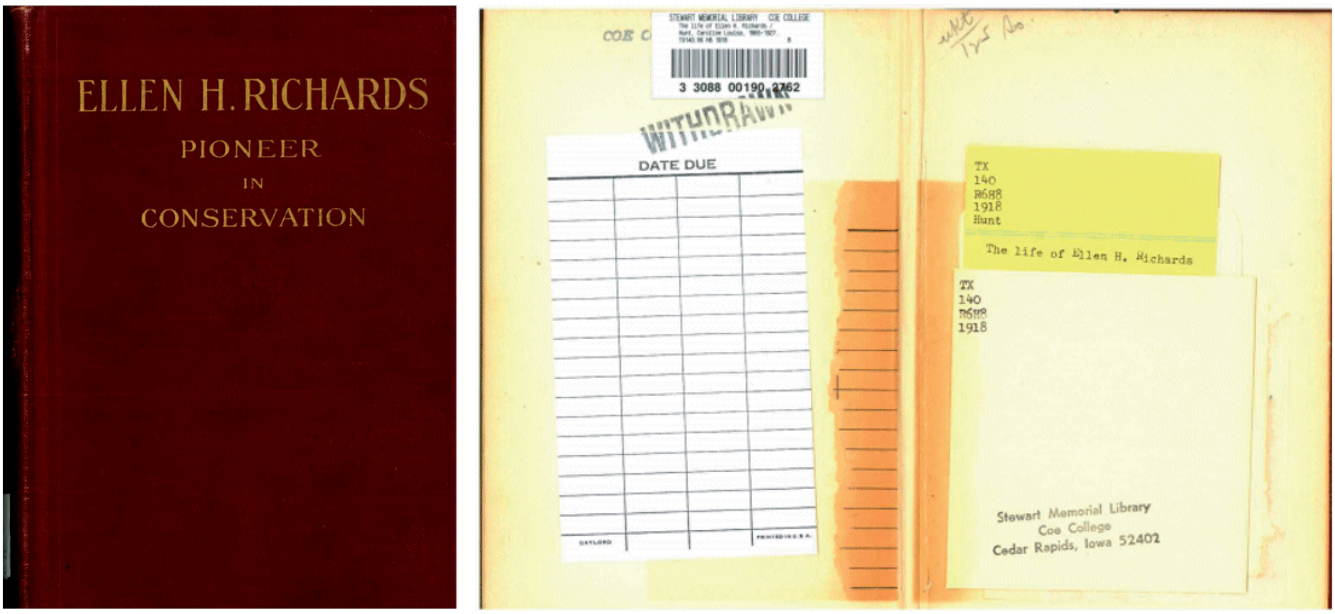

Figure 5: Biography of Ellen (Swallow) Richards – never removed from the library and withdrawn (Rawle own copy).

An early book on Ellen (Caroline L Hunt "The Life of Ellen H. Richards" Whitcomb & Barrows, Boston (1918)) – my copy was never removed from the library – is also recommended.

Ellen was the first woman admitted to any scientific school in the United States and the first female graduate of MIT. She was the first woman to be elected to the American Institute of Mining Engineers. She was also elected a fellow of the American Association for the Advancement of Science, an unusual honor for that time. She developed courses of study, set standards for the training of teachers, organized a professional organization, and edited a journal. The research that she and her colleagues had done clearly showed that exposure to contaminated air, water, food, and soil made people sick. She believed that people had a right to know what they were breathing, drinking, and eating. In a forward-looking speech she wrote:

> *The quality of life depends on the ability of society to teach its members how to live in harmony with their environment — defined first as the family, then with the community, then with the world and its resources.*

In the last decade of her life, she earned a substantial income from teaching, writing, and consulting. When she died of heart disease at the age of 68, she left virtually no estate. She had given all her money away.

As a part of the Massachusetts exhibit at the Chicago World's Fair in 1893, Mrs. Richards operated a "Rumford Kitchen," named for the Yankee-born Count Rumford who had pioneered the science of nutrition. Visitors could watch the expert preparation of food and buy 979.3 calories' worth of baked beans, brown bread, butter, and apple sauce for thirty cents. See: http://www.jphs.org/people/2005/4/14/ellen-swallow-richards-the-first-oekologist.html

The food was served in portions containing a definite amount of nutrition, and the menu card on each table gave the requirement for one-quarter of one day's ration, with the weight and composition of each dish composing the meal. A choice of two or three luncheons, for which the price was thirty cents, was given each day, each containing three or four dishes, though an extra price was made for a glass of milk, for a cup of cocoa, tea or coffee. See: https://libraries.mit.edu/archives/exhibits/esr/esr-rumford.html

In Hunt's book (see above: pages 220 and 221) it is stated "The man, too, from Southern Europe who defiantly said, "You needn't try to make a Yankee of me by making me eat that," pointing to baked Indian Pudding..." I ate Indian Pudding at Durgin Park Restaurant, Boston after my US Naturalization ceremony in Faneuil Hall, Boston in 2008.

One of her main claims to fame though, was in detailed water analyses of Massachusetts. From 1884 until her death, Ellen was an instructor in the newly founded laboratory of sanitary chemistry at the Lawrence Experiment Station, the first in the United States and headed by her former professor, William R. Nichols.

Figure 6: Ellen 'Nellie' Swallow and Robert Richards (Courtesy MIT Museum)
Original url: http://libraries.mit.edu/archives/exhibits/wbr-visionary/

In 1887, the laboratory, directed by Thomas Messenger Drown, conducted a study under Richards of water quality in Massachusetts for the Massachusetts State Board of Health involving over 20,000 samples, the first such study in America. Her data was used to find causes of pollution and improper sewage disposal. As a result, Massachusetts established the first water-quality standards in America and its first modern sewage treatment plant at Lowell, Massachusetts. She was a consulting chemist for the Massachusetts State Board of Health from 1872 to 1875 and the Commonwealth's official water analyst from 1887 until 1897.

Ellen was a founding ecofeminist who believed that women's involvement within the home was a vital aspect of the economy. Her interests in this regard included applying scientific principles to domestic situations, such as nutrition, clothing, physical fitness, sanitation, and efficient home management, creating the field of home economics. But she was also a pragmatist, saying "You cannot make women only contented with cooking and cleaning, and you need not try." See: http://www.usasciencefestival.org/schoolprograms/2014-role-models-in-science-engineering/751-ellen.html

Figure 7: Note the woman with the ax – bottom left (Courtesy: MIT Museum). Ellen Richards is at the far top left.

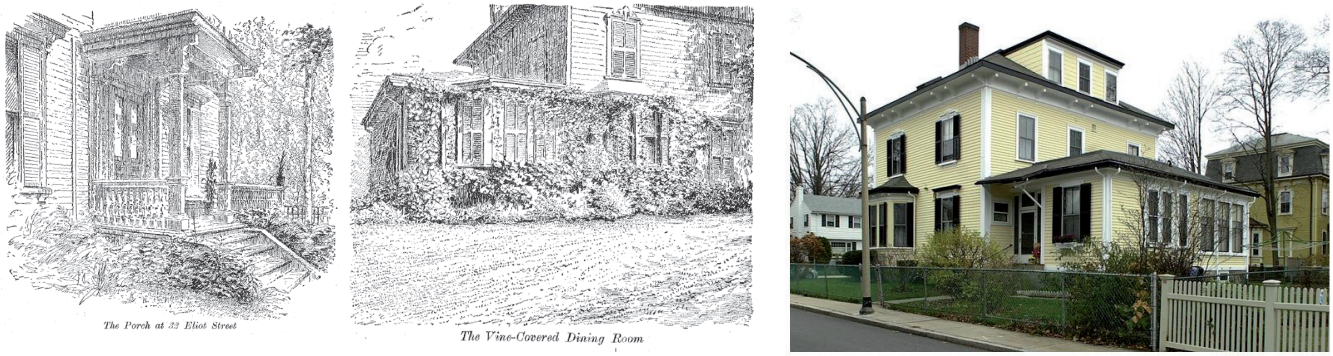

Figure 8: 32 Eliot Street, Jamaica Plain, Boston First 2 drawings from Drawings from Ellen H Richards' biography and last picture from Google Streetview

Their house ("rented and later bought") - 32 Eliot Street, Jamaica Plain, Boston - became an important icon. The house was added to the National Register of Historic Places and declared a National Historic Landmark in 1992 (the Ellen Swallow Richards House). In her honor, MIT designated a room in the main building for the use of women students. In 2023 the address was up for sale at approximately $2.1 million.

In "His Mark" pages 157 – 158, Robert Richards states: " It was my wife's idea to build an addition to our dining room, in order to have sufficient room for the students who used to visit us". "When we first moved to 32 Eliot Street, there was an old well under the corner of the kitchen. It was necessary to pump water by hand into a tank in the attic for the bathroom upstairs. We had city water about 1878. From the start we had gas for light, and after a while bought a gas stove".

In 1973, on the occasion of the hundredth anniversary of Richard's graduation, MIT established the Ellen Swallow Richards professorship for distinguished female faculty members. In 2011, she was listed as #8 on the MIT150 list of the top 150 innovators and ideas from MIT.

Nellie died comparatively young of the same heart ailment as Vezin and was buried in Gardiner, Maine. Robert followed much later in 1946 and was buried next to her. Shortly after Nellie's death, Robert married Lillian Jameson, a former secretary to Ellen. Lillie (born July 14, 1866) died on March 31, 1924, but is buried in Woodbrook Cemetery, Woburn, Middlesex County, Massachusetts. W T Sedgwick in an eulogy entitled "Mrs. Richards' Unique Position: An appreciation of her work at the Institute by Prof. Sedgwick" Boston Transcript, March 31, 1911 stated: "Many gaps left by death are not difficult to fill, but this is not the case with Mrs. Richards. Her position in the Institute and her work in the world were both unique. No one can fill her place. Other women may become experts in water analysis and preside over laboratories, but no one hereafter can possibly gain the peculiar historic equipment which fell to Mrs. Richards. Other women may, and no doubt will, make addresses and write books upon sanitation and the home, but no one else can ever do these things as Mrs. Richards has done them, for the reason that she was herself an evolution and represented an epoch. We are always too prone to undervalue things familiar and near at hand, and Boston and Massachusetts have never adequately appreciated Mrs. Richards or her work. But now that she is gone and no one can possibly take her place, we may begin to realize the extent of our loss".

On August 26, 1944, Roberts Richards celebrated his 100th birthday. He was 100 years old. Interestingly, 10 years earlier on August 26, 1934, he had celebrated his 90th birthday. In his autobiography (page 278), Richards tries to explain in a humorous fashion how he managed to reach that grand old age: "After doing all the things I could think of to help me live to 90 years old, I finally said, "Why do we men have to have our shoulders all covered up when the girls are going with their low necks and short sleeves which toughen them so finely?" So, I started going to bed without any body clothes on, to come as nearly as possible to the girls' result. Upon which, when my lovely opposite girl neighbor heard of it, she wrote:

"I wear my pink pajamas
In the summer when it's hot
I wear my flannel nightie
In the winter when it's not
Sometimes in the springtime
And sometimes in the fall
I jump right in between the sheets
With nothing on at all"

Earlier in the text, he outlined his philosophy for health:

Food
Exercise
Amusement
Sleep
Task (or work)

I suspect that this was really Ellen Swallow's statement taken from her home economics courses.

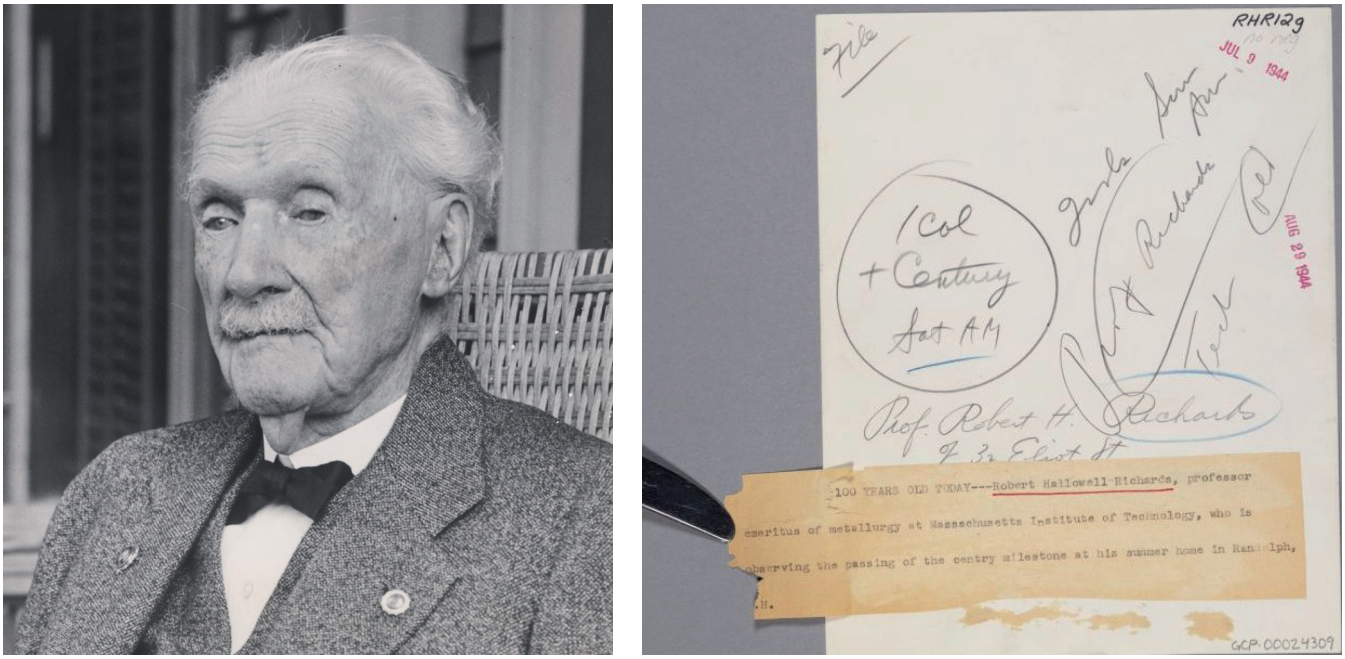

Figure 9: Robert Richards on his 100th birthday (courtesy MIT Museum GCP-00024309).

Robert Hallowell Richards died on March 27, 1945, and is buried next to his first wife (and soul mate), Ellen Swallow in Christ Church Cemetery, Gardiner, Kennebec County, Maine close to his birthplace. Lillian Jameson, who died on March 31, 1924, in Washington DC is buried separately in Woodbrook Cemetery, Woburn, Middlesex County, Massachusetts.

AIME honored Dr. Richards' memory in 1948 by establishing the Robert H. Richards award as the premier award in the field of ore processing.

Further Source Material

In 1946, AIME published a classic volume ('Richards Memorial Volume' No. 169) on Milling and Concentration with a biography written by one of his former students, Frank E. Shephard, mainly based on extracts from Richards' autobiography. This volume contains 2 classic papers (one by Fred Bond and one by Risto Tapani (R T) Hukki – with Gaudin) on comminution. An earlier biography was written by Arthur Winslow in July 1908 to commemorate Richards' 40 years of service to MIT. This was published in 'The Technology Review' (the official MIT journal) Volume X No. 3 249 – 257 with a facing portrait at the beginning.

For Ellen Swallow Richards, see: "Ellen Henrietta Richards, A.M., Sc.D.: A biographical sketch of her life - Her remarkable career and her many public activities" MIT Technology Review Volume XIII, 365-373, (1911) plus the many biographies (Google or Abebooks search!).

A publications list for Ellen Swallow Richards is shown at: http://libraries.mit.edu/archives/exhibits/esr/esr-bibliography.html

ACKNOWLEDGEMENTS

I'd like to give my heartfelt thanks to Elias Trout, MIT Museum and Amanda Hawk, MIT Libraries - Distinctive Collections, for their rapid responses to my inquiries and tracking down the true lineage of a couple of the figures.

WCSB12 – Sampling for a Sustainable World

DOI: 10.62178/sst.004.011

We are pleased to announce that WCSB12, originally scheduled to take place in summer 2026 in Cornwall (UK), has been relocated to Burlington House, Piccadilly, London on 25-27th November 2026.

The conference will be organised by the Geological Society of London.

WCSB12 aims to bring together the diverse international sampling community to present and debate concepts and ideas for a standardised approach to sampling embodied in the Theory of Sampling (TOS).

The opportunity to meet, exchange ideas, and share practical experiences will be a significant benefit for attendees. The Conference will provide understanding and insights for practitioners, academics, manufacturers and engineering firms aiming to achieve representative sampling through TOS.

WCSB12

25th to 27th November 2026
Geological Society of London , Burlington House, Piccadilly, London, UK.

We look forward to meeting in the new location to explore and discuss the new frontiers of sampling and blending!

For updated information, stay tuned on the IPGSA and GSL webpages: intsamp.org and geolsoc.org.uk

Contributors

Esbensen, Kim H.

Dr Kim H. Esbensen has been research professor in Geoscience Data Analysis and Sampling at GEUS, the National Geological Surveys of Denmark and Greenland (2010–2015), chemometrics and sampling professor at Aalborg University, Denmark (2001–2015), professor (Process Analytical Technologies) at Telemark Institute of Technology, Norway (1990–2000 and 2010–2015). From 2015 he phased out a 35 year academic career for a new quest as consultant and independent researcher. But as he could not terminate his love for teaching, he is regularly active as an international visiting, guest and affiliate professor. A geologist/geochemist/metallurgist/data analyst of training, he has been working 20+ years in the forefront of chemometrics, but since 2000 has devoted most of his R&D to the theme of representative sampling of heterogeneous materials, processes and systems: Theory of Sampling (TOS), PAT (Process Analytical Technology) and chemometrics. He is a member of several scientific societies and has published over 250 peer-reviewed papers and is the author of a widely used textbook in Multivariate Data Analysis, which was published in its 6th edition in 2018. He was chairperson of the taskforce behind the world's first horizontal (matrix-independent) sampling standard DS3077 (2013), 3rd. ed. soon to be inducted as an ISO standard. In 2020 he published the foundational "Introduction to the Theory and Practice of Sampling". Since 2013, he was editor of TOS forum and Spectroscopy Europe/World "Sampling Column", from 2024 amalgamated and metamorphosed into "Sampling Science and Technology" (SST). Kim received the Pierre Gy Gold Medal in 2013 and received the IPGSAs first Distinguished Service Medal in 2024.

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Dusko Kadijevic is a laboratory manager and process analytics consultant with more than 17 years of experience in industrial analytical technology, quality control, and process optimization. After many years at BASF in various analytical and process development roles, he joined Menzel Metallchemie as head of laboratory, focusing on automation, lubricant development, and the implementation of efficient analytical workflows.

As founder of Consulting-DK, he advises companies on process analytical technology (PAT) and digital transformation in laboratory and production environments. His work emphasizes the practical integration of sensors, automation, and data-driven decision systems to improve process understanding, reliability, and economic performance. He also contributes to the dissemination of applied sampling science as a supporting framework for robust analytical design.

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Kurth, Henry

Henry Kurth is a geologist with 15 years in mining geology in base metals, gold and coal. The roles involved volcanogenic massive sulphides in Tasmania, SEDEX Mount Isa lead-zinc and copper, gold at Norseman in the Western Australian Goldfields, and coal in Queensland's Surat Basin. This provided exposure to existing sampling practices and understanding by mining professionals and much frustration with process professionals. After several technical sales roles with chemical companies over seven years, Henry found a niche at Scantech International Pty Ltd where he grew the company's real time analysis technology sales in the minerals sector to the current world-leading position. With 19 years at Scantech, he is currently Chief Marketing Officer and Minerals Consultant helping clients with real time measurement solutions for mined ore quality and expanding applications into the growing recycling sector. The proven solutions for continuous and representative conveyed material compositional analysis have many operational benefits he could only dream of as a mine geologist.

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Møller, Hans S.

Hans Møller holds an MS in physics and chemistry. As a chemical engineer at Danish thermal power plants, he has worked on many aspects of analytical chemistry. When coal became the main fuel for Danish power plants, he got involved in designing and operating mechanical sampling systems for hard coal, which were established at all power plants and the coal import harbor. These systems were designed according to the principles of ISO 13909, a standard Denmark helped develop from 1985 to 2009. Over time, he established the field of Applied Tribology, focusing on lubrication issues in large industrial facilities like steam and gas turbines, thermal power plants, and power transformers. Wind energy has long been a key part of Denmark's industry, with companies like Vestas and Siemens, and he has contributed to many studies on lubricating oils in wind turbine gears, recently developing advanced methods for condition monitoring of grease-lubricated main components in wind turbines. A common challenge across these activities is obtaining representative samples, whether for acceptance testing of steam coal, hydraulic oils from turbines, or grease from main and blade bearings in wind turbines. Today, he is a co-owner of TriboTech, a company providing Applied tribology consulting services to a wide range of energy companies.

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Rawle, Alan F.

In May 2024, Alan Rawle put down (or hung up) his spatula, scoop, and spinning riffler (3 Sampling S's) for the last time after 34 years tied to the particle characterization industry, a topic he'd first encountered in his Ph.D. at the very end of the 70's (not his 70's but the 1970's). He has now taken up a full-time career in cat herding and bird watching. In the context of contributing articles to magazines, his nom-de-plume is Phil Space. Alan has a degree in industrial chemistry and a Ph.D. in supported alloy catalysts, both acquired at Brunel University, London, UK. From 1990 to 2024, Alan was with Malvern Instruments (now Malvern Panalytical) and was the Applications Manager based in Westborough, MA, USA since 2003. Dr. Rawle had spent many years working with the ISO TC24/SC4 (Particle Characterization) standardization committee, assisting with the writing of documentary standards in light scattering, small-angle X-ray scattering, image analysis, zeta potential, and dispersion, as well as his own interest in the theory and practice of sampling. He presented Short Courses at Pittcon for over 10 years on these topics. Dr. Rawle was (2005 – 2022) Co-Chair of E 56.02, the Characterization SubCommittee of the ASTM E56 Committee on Nanotechnology. He was the Technical Author (i.e., writer) for ASTM standards in particle sizing, zeta potential, size distribution calculation, among others. In 2023 Alan received ASTM's highest honor - the Award of Merit - and is thus a Fellow of ASTM (FASTM). Dr. Rawle is also a Fellow of the Royal Society of Chemistry (FRSC), a Distinguished Fellow of the International Engineering and Technology Institute (DFIETI), and a regular contributor to ResearchGate.

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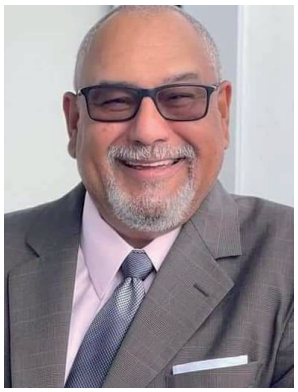

Ritchie, Gary E.

Gary is an internationally recognized expert In pharmaceutical analysis with a focus on vibrational spectroscopy and multivariate analysis, process analytics, quality control, and assurance, Gary's experience includes increasing responsibilities in quality control, technical services, research and development and new technologies with Schein Pharmaceuticals and Purdue Pharma. Gary served as Scientific Fellow for Process Analytical Technology and Liaison to the General Chapters, Pharmaceutical Waters and Statistics Expert Committee's from 2003 through 2008 for the United States Pharmacopeia (USP). Gary served as Director of Scientific Affairs for InfraTrac from 2009 through 2015, and Directir of Operations for Dynalabs feom 2015 to 2017. Currently, Gary serves as a consultant with GER Compliance. Gary has more than twenty-five peer reviewed papers and book chapter contributions; four issued patents, numerous industry journal articles, and has been invited to give conference and symposia presentations worldwide. He was President of The Council for Near-Infrared Spectroscopy (2012-2014). Gary's combined experience in industry and regulatory agencies has allowed him to quickly see through problems and provide solutions. Gary has a deep appreciation for pharmaceutical regulatory science. This coupled with his hands on experience in pharmaceutical and process analysis allows him to provide solutions that are both practical and compliant. Gary has demonstrated leadership and organization skills at both the domestic and international levels, having led a 47 member consortium of pharmaceutical industry and regulatory bodies to revise a national standard for the USP. He has chaired committees for the ASTM International and the International Diffuse Reflectance Conference (IDRC). Gary received his Bachelor of Arts and Masters of Science in Biology at the University of Bridgeport, Bridgeport, Connecticut.

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Romañach, Rodolfo

Dr. Romañach is Professor of Chemistry at the University of Puerto Rico – Mayagüez Campus. He worked in the pharmaceutical industry for over 12 years before joining the Chemistry Department in 1999. He achieved his mission of training a new generation of pharmaceutical scientists capable of moving the analytical chemistry laboratory into the manufacturing area. His research is described in over 140 publications. He now wants to develop stronger industry and university collaborations.

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Swarbrick, Brad

Brad Swarbrick is the Managing Director and cofounder of KAX Group, an global company that provides multivariate data analysis (MVDA) software and solutions for a number of industries, mainly focussed on pharmaceutical applications of Chemometrics, PAT and QbD when applied to spectroscopic and process data.

Brad has over 25 years of experience in the application of Chemometrics and Design of Experiments (DoE) methodology in a wide range of industries, including agriculture, petrochemical and pharmaceuticals. Until recently, Brad was the Chief Operating Officer of a world leading provider of the Chemometrics software prior to founding KAX Group where he successfully brought a number of new software developments and large projects to commercial reality. Brad worked in the pioneering Pfizer Process Analytical Technology (PAT) group, developed the entire NIR program for Sigma (now Aspen) pharmaceuticals and worked as a GMP consultant for one of SE Asia's largest pharmaceutical consultancy groups.

Brad has a unique combination of technical and business skills that have allowed him achieve the many business objectives that his clients are now enjoying. Brad is a globally recognized expert trainer in Chemometrics and Design of Experiment methodology and has many years of expertise in Near-infrared (NIR) spectroscopy and Process Analytical Technology (PAT). Brad is the current section editor of pharmaceuticals, for the Journal of Near Infrared Spectroscopy, has co-written the well-known Multivariate Data Analysis in Practice (6th Edition) with Professor Kim Esbensen and has also written a number of textbook chapters on NIR and Chemometrics, in particular the popular short book "Multivariate Analysis for Dummies" and most recently has contributed two chapters on NIR spectroscopy and Chemometrics into the Handbook of Measurement in Science and Engineering (Volume 3).

Brad has a Ph.D. in Biospectroscopy and Advanced Chemometrics and also holds a Bachelor of Science degree, majoring in Chemistry and an honours degree in Chemometrics.

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How to contribute

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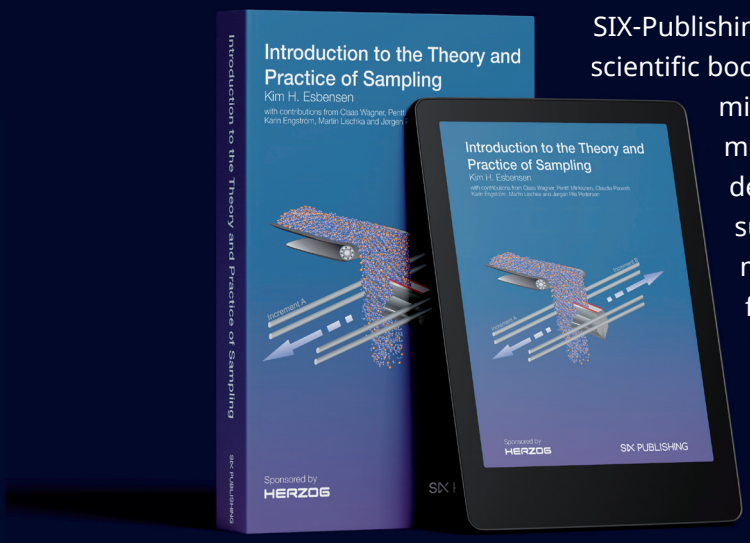

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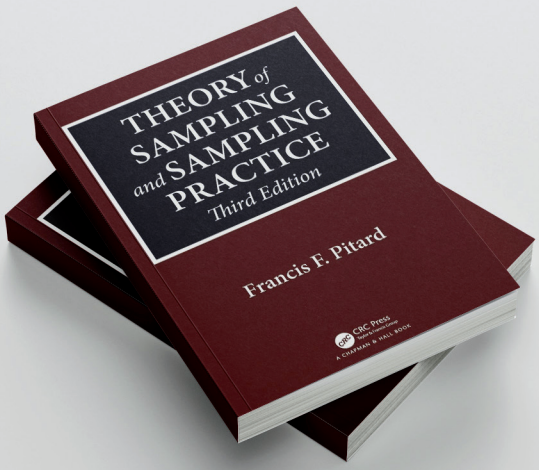

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