March 2017

Lab Manager®

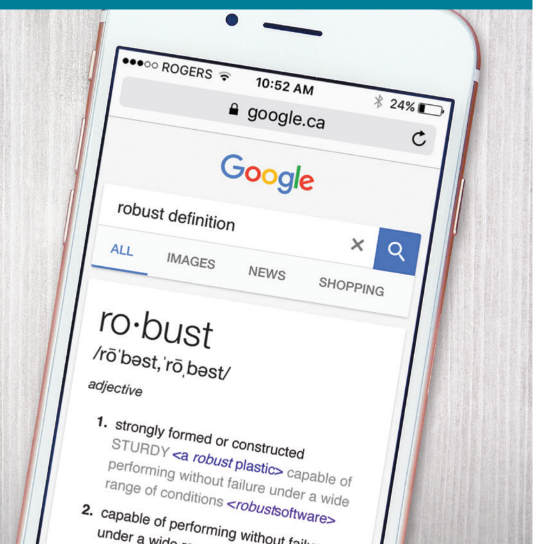
Run Your Lab Like a Business

LabManager.com

ANALYTICAL ROBUSTNESS

HOW ROBUST INSTRUMENTS AND WORKFLOWS CAN OPTIMIZE LAB TESTS AND PROCESSES

by Paul Voelker, Thermo Fisher Scientific



Manufacturers of analytical instruments often use robustness as a selling point, but what do they really mean when they say their hardware is robust? Likewise, much emphasis is placed on the importance of robustness in laboratory information management systems (LIMS), but how do these systems deliver reliable performance in spite of process variability?

In this article, we look at three commonly used analytical techniques—ion chromatography (IC), gas chromatography (GC), and inductively coupled plasma mass spectrometry (ICP-MS)—to better understand why robustness matters when it comes to analytical measurements and how instruments can be designed with robustness in mind. We also consider the laboratory processes associated with these techniques, such as sample and workflow management, to understand how robust LIMS can optimize performance and deliver financial benefits.

What is "robustness"?

Robustness. It's a powerful word that's more likely to conjure up images of Arnold Schwarzenegger in an armored tank than of an analytical laboratory. Much is written about the value of robustness in analytical instruments, but less on how it is defined and the impact it has on optimization of laboratory tests and processes. In fact, laboratory robustness has a number of interpretations, the most important of which relate to measurements, instruments, and processes.

A robust measurement is one that is both sensitive and precise. Sensitivity refers to an instrument's ability to detect a change in signal, and precision means that measurements are reproducible.

Instrument robustness plays a vital role in delivering accurate results on time and on budget. Does your equipment operate reliably under expected process conditions such as temperature changes, dust, solvent exposure, and vibration? If, like Arnold's tank, it can handle anything the world throws at it, it's safe to say it's pretty robust.

It's also important for wider laboratory processes and methods to be robust too. Robust processes are those that yield a specific product or result that meets the required specifications in spite of normal fluctuations in process variables. Put another way, can a laboratory workflow handle change? Does it work efficiently? Can you count on the workflow to deliver the required goods?

Here we consider how each of these interpretations applies to an analytical laboratory and the value robustness brings in each case.

How does robust hardware produce "better" measurements?

Robust measurements are reliable

To illustrate the importance of process robustness, here we discuss the United States Pharmacopeia-National Formulary (USP-NF) assay for trace detection of ammonia in sodium bicarbonate.[1]

Sodium bicarbonate is used for a wide variety of pharmaceutical applications—one of the most common being hemodialysis. Ammonia is one of the impurities that is assayed, as its presence in the bloodstream can cause adverse effects. In the current USP-NF monograph for sodium bicarbonate, ammonia is measured by a colorimetric assay based on its reaction with phenol under alkaline conditions in the presence of hypochlorite and sodium nitroferricyanide (a strong oxidizing agent). The reaction results in the formation of a blue-green complex, indophenol blue. The assay's acceptance criterion is that "no blue color develops" in one hour, equivalent to a 0.002 percent detection limit in sodium bicarbonate.[1] However, this colorimetric assay is subjective, necessitates caution in handling and storing the strong oxidizing agent, and requires that waste is not exposed to acidic conditions that can liberate poisonous cyanide gas.

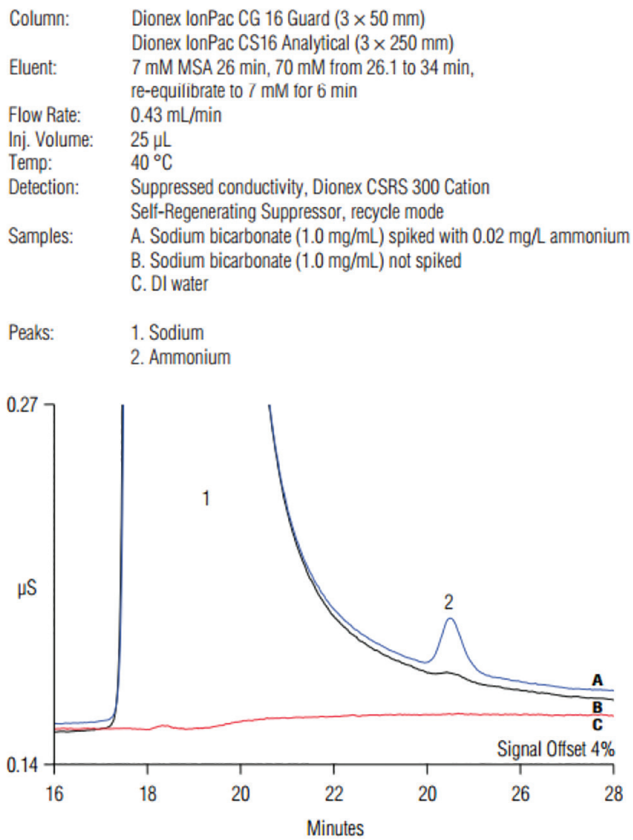
An alternative IC-based analytical approach was recently developed[2] that is capable of accurately determining ammonia levels in sodium bicarbonate at this detection limit. For sodium bicarbonate, the cation at high concentration is sodium, which elutes close to ammonia and therefore makes its determination challenging (Figure 1). However, a Thermo Scientific™ Dionex™ IonPac™ CS16 high-capacity cation-exchange column and a methane sulfonic acid eluent can detect ammonia despite small variations in the method parameters (Table 1).

In these experiments, peak asymmetry ranged from 1.2 to 1.3, and resolution of ammonia relative to sodium ranged from 5.17 to 5.69. This analytical robustness means reliable results can be obtained even under fluctuating operating conditions.

Robust instruments can handle almost anything

Radio frequency (RF) generators play an integral role in the determination of trace elements by ICP-MS. This method employs high-purity argon and an oscillating RF field to sustain a plasma that is used as an atomization and ionization source during analysis.

The challenge of RF generators is adjusting quickly to changing conditions in the plasma due to differing sample matrices such as high metal or salt content or organic solutions. Depending on the design, certain solid-state RF generators can respond much more rapidly to changing matrices. These fast reaction times enable the plasma intensity to quickly stabilize, resulting in a steady-state signal almost immediately after the sample is introduced. This robust *instrument* performance allows the analyst to tackle a variety of matrices and a high number of samples with minimal QC failures, sample reruns, and instrument downtime.



Conditions	Sodium	Ammonium			
	Retention Time (min)	Retention Time (min)	Relative Retention Time (relative to sodium)	Resolution (relative to sodium)	Asymmetry
Flow Rate 0.43 mL/min, 40 °C, 7 mM MSA	18.85	24.46	1.4	5.50	1.22
Flow Rate 0.38 mL/min, 40 °C, 7 mM MSA	21.25	27.54	1.0	5.51	1.27
Flow Rate 0.48 mL/min, 40 °C, 7 mM MSA	16.88	21.83	1.3	5.24	1.31
Flow Rate 0.43 mL/min, 38 °C, 7 mM MSA	19.04	24.83	1.3	5.69	1.18
Flow Rate 0.43 mL/min, 42 °C, 7 mM MSA	18.68	24.11	1.3	5.37	1.26
Flow Rate 0.43 mL/min, 40 °C, 5 mM MSA	25.19	32.88	1.3	5.55	1.25
Flow Rate 0.43 mL/min, 40 °C, 9 mM MSA	15.28	19.64	1.3	5.17	1.31

▲ *Table 1: Robustness towards varying analytical conditions*

Robust laboratories offer workflow flexibility

Analytical instruments require the flexibility to handle a variety of analyses. They often need to operate continuously, despite scheduled maintenance periods. Laboratories can benefit from modular instrument systems, which allow reconfiguration of workflows for specific analytical tests and easy replacement of instrument parts. Therefore, it is important that these instrument modules are easily removable and can be reinstalled without impacting analytical performance.

In a robustness *measurement* study of Thermo Scientific Instant Connect modules that form part of the Thermo Scientific TRACE™ 1300 Series GC system, the injector module was repeatedly removed from and reinstalled in the system by a range of personnel, including nonspecialists.[3] Throughout the study, no variation in retention time or peak area was observed in the analysis of a hydrocarbon test mix. Similarly, replacing the detector module with a second identical unit had no significant effect on analytical performance. This experiment highlights the reliability and robustness that compact, modular instruments can offer laboratories that require workflow flexibility.

How do robust processes offer benefits in the lab?

The above-mentioned case studies highlight how robust instruments and analytical methods can handle fluctuations in experimental conditions to provide analysts with reproducible and reliable results. Yet scientists are also a source of process variability.

In the laboratory, all data, from sample volume to equipment status, must be recorded, stored, and analyzed correctly. Testing procedures, such as those based on chromatography, typically require compliance with exacting specifications in order to meet regulatory standards. Even the smallest error can have far-reaching consequences. Failure to process even a single sample according to standard operating procedures

	nC10	nC12	nC14	nC16	nC18	nC20	nC22	nC24	nC26	nC28	nC30	nC32	nC34	nC36	nC38	nC40
Injection 9 before IC swap	2754987	2779540	2709468	2720590	2662466	2694642	2671418	2666034	2640542	2660383	2748956	2756412	2705301	2768808	2658421	2670870
Injection 10 before IC swap	2751265	2775027	2708032	2732281	2677453	2705799	2688053	2684329	2667261	2684684	2755387	2771243	2709754	2772642	2651536	2665536
Injection 1 after IC swap	2767372	2791927	2719553	2738439	2664499	2693367	2672357	2657758	2643338	2655810	2738028	2745997	2704789	2768416	2664390	2670998
Injection 2 after IC swap	2756768	2787601	2711585	2738364	2687682	2720242	2699762	2690563	2663741	2677520	2756966	2774421	2711745	2765971	2664631	2676359
Variation	-0.59%	-0.61%	-0.43%	-0.23%	0.48%	0.46%	0.58%	0.99%	0.90%	1.08%	0.63%	0.91%	0.18%	0.15%	-0.48%	-0.20%

▲ *Table 2: Variation in peak area before and after 100 times injector module replacement cycle*

	nC10	nC12	nC14	nC16	nC18	nC20	nC22	nC24	nC26	nC28	nC30	nC32	nC34	nC36	nC38	nC40
Injection 9 before IC swap	2.562	3.935	5.253	6.447	7.525	8.507	9.408	10.235	11.003	11.717	12.383	13.010	13.598	14.153	14.678	15.185
Injection 10 before IC swap	2.563	3.933	5.255	6.445	7.523	8.508	9.407	10.237	11.005	11.717	12.383	13.012	13.595	14.154	14.677	15.185
Injection 1 after IC swap	2.563	3.935	5.253	6.447	7.525	8.507	9.408	10.238	11.003	11.718	12.385	13.010	13.598	14.153	14.678	15.183
Injection 2 after IC swap	2.563	3.935	5.253	6.447	7.523	8.508	9.407	10.237	11.003	11.718	12.385	13.012	13.600	14.155	14.680	15.187
Variation	-0.03%	-0.04%	0.04%	-0.03%	-0.02%	0.01%	-0.02%	-0.02%	0.02%	-0.01%	-0.01%	0.02%	-0.02%	0.00%	-0.01%	0.01%

▲ *Table 3: Variation in retention time before and after 100 times injector module replacement cycle*

(SOPs), for instance, could lead to delays in production, a noncompliance penalty, or reputational damage, as well as an associated financial cost.

LIMS can help laboratories operate consistently according to predetermined SOPs. Software management systems minimize differences in instrument setup and data analysis by automating and simplifying laboratory workflows. They can also perform standard, quality control, and system suitability calculations and use real-time data to make intelligent decisions in the middle of a sequence. These decisions can be used, for instance, to stop an analytical run should these tests fail against user-defined criteria—saving time and resources.

Instrument maintenance is integral to the smooth running of a laboratory. Failure to detect and report the warning signs of instrument failure can have severe effects on analytical performance and even halt production entirely. LIMS allow users to monitor instrument health in real time and serve as an early warning system for processes that are out of sync with the established SOP. For instruments that need routine attention, LIMS allow preventive maintenance to be scheduled and executed in advance of failure. This way, work can be planned more effectively around a regular maintenance schedule, and users can be notified of upcoming maintenance.

Another area where human error can have a serious impact on laboratory productivity is inventory management. An inability to anticipate future needs can result in costly production delays, and expediting shipments of out-of-stock consumables can be expensive. LIMS help laboratories develop more robust processes for tracking and budgeting for consumables, and they can send out timely stock level alerts. Improved inventory management allows laboratories to reduce waste and eliminate production delays, increasing efficiency and profits.

Finally, LIMS provide a secure environment for long-term data archiving related to sample testing and workflow, ensuring that any request for data can be accommodated at any point in time, whether for standard internal reporting or for industry or regulatory audits. Having an enterprise-level LIMS integrated not only with the lab instrumentation and equipment but also with existing enterprise systems (such as PIMS and LES) ensures that secure data is available when it is needed.

Conclusions

Robust analytical instruments and workflows are improving process reliability in the lab. The latest laboratory hardware can be designed with robustness built in, providing scientists with sensitive, precise measurements despite fluctuations in experimental and environmental conditions. Robust technology is also giving laboratories increased workflow flexibility, and it can be combined with intelligent systems to help boost efficiency and more effectively manage instrument downtime. These advances in laboratory reliability are driving improvements in productivity and profitability.

References

1. Sodium Bicarbonate. U.S. Pharmacopeia; Rockville, MD, USP35.
2. Basumallick, L. and Rohrer, J.; Determination of Ammonia in Sodium Bicarbonate. https://tools.thermofisher.com/content/sfs/brochures/AN-1073-Determination-Ammonia-Sodium-Bicarbonate-AN70815-E.pdf
3. Pigozzo, F. and Magni, P.; Analytical Repeatability, Accuracy and Robustness of Instant Connect GC Modules. https://www.thermofisher.com/content/dam/tfs/ATG/CMD/cmd-support/trace-1300-series/operations-and-maintenance/technical-bulletins/Analytical-Repeatability-Accuracy-and-Robustness-of-Instant-Connect-GC-Modules.pdf

__Paul Voelker__ is the vertical marketing manager for the environmental and industrial markets in chromatography and mass spectrometry at Thermo Fisher Scientific. He can be reached at paul.voelker@thermofisher.com