NOVEMBER 2013 # 10

the Analytical Scientist

Orbitrap Against All Odds

Inventor Alexander Makarov's tale of perseverance, luck and, ultimately, success

24 – 30

Webinar

Virtual Events

Making the GC-MS Triple Transition with Ease

Register Free at:
http://tas.txp.to/0913/802/reg

Event Overview:

Are you considering the transition from single quadrupole GC-MS to triple quadrupole GC-MS in your lab? Due to the numerous benefits offered by this technique, many labs are adopting it and making it the fastest growing technique in GC-MS. Moving your current GC-MS methods from single quadrupole GC-MS platforms to triple quadrupole GC-MS offers many advantages that ultimately provide excellent method performance and optimized laboratory workflows. Today, the technique is more accessible than ever with many tools available to remove complexity, promote automation, and enable your lab to focus on real result production – regardless of the skill level of the user.

During this event, we will discuss the basics of the technique, how it enables optimized workflows, and how you can easily adopt this technology into your lab with the greatest ease.

Key Learning Objectives:

1. Understand the basic aspects of triple quadrupole GC -MS and the common terms used
2. Learn how the technique can be applied to improve laboratory workflows, as well your analytical results
3. Discover how to ease the adoption of triple quadrupole GC-MS into your lab

Speakers
Paul Silcock
Marketing Manager, Triple Quadrupole GC-MS
Thermo Fisher Scientific

Cristian Cojocariu
Senior Applications Specialist, Triple Quadrupole GC-MS
Thermo Fisher Scientific

Moderator
Rich Whitworth

Date
17/12/13 - 08:00 (Pacific Standard Time)

Presented By
the Analytical Scientist

Sponsored By
ThermoFisher SCIENTIFIC

Online this Month

Care to Comment?

Publication of articles is often the starting point for an informed debate. Here's a flavor of recent discussions on our website:

Quality Education (tas.txp.to/1013/quality)

"4.1.5 of the ISO 17025:2005 standard says:

g) provide adequate supervision of [...] staff

k) ensure that its personnel are aware […] and how they contribute to the achievement of the objectives of the management system.

So, by my reading, if your staff don't know what 17025 is for and how it helps the organization, and if your staff are using cheat sheets then you already have two non-conformities. – *Technical Manager of a 17025 accredited Testing Laboratory*

"The ISO 9001:2008 standard requires an organization to define its processes and the interrelationship between the processes. Using this same process principle, the lab manager should develop and maintain standard operating procedures (SOPs) beginning with interconnected steps for all steps involved using process mapping techniques. Define all process steps,decision points and 'what if' steps. Once the steps involved in the SOP are defined and finalized with all inputs and outputs of the process, be sure to use pictures, symbols, icons, etc., that are relevant to the process in documenting the SOP. Icons and pictures reduce the likelihood of users misunderstanding the SOP. Finally, the SOPS need to be written to inform, not to impress, keeping the users needs in mind throughout the process." - *Jerome Council, ASQ-CQA, CBA*

History Lesson (tas.txp.to/1013/chemometrics)

In ancient times (1971), chemometrics followed two separate paths - supervised learning using learning machines, PCA for example, and unsupervised learning using clustering machines. K-nearest neighbors (KNN), minimal spanning tree and other tree variations were key methodologies, which have placed chemometrics into the modern realm of graph theory. Various spanning tree models have been critical in studies of genomics and other fields where your needle in a haystack analogy has long been valid. Retracing early chemometric works by Bruce Kowalski, Peter Jurs and Svante Wold might provide some leads to these now seldom used methods. By the way, the word chemometrics, was coined by Svante Wold and his research group at Umea who started calling their work 'chemometrics' some time in the very early '70s (source: www.namics.nysaes.cornell.edu). - *Doug Dierdorf*

Sign up online for free to have your say:
theanalyticalscientist.com/subscribe

Twitter List

The Power List generated questions, profundities and celebration in the Twittersphere…

Oct 30 @ejanemaxwell: *GMW on being #3 on the @tAnaSci #PowerList: " Dear colleagues: Did you realize you were analytical chemists?"*

Oct 29 @scrippsresearch: *Congrats John Yates! Scripps Research biology professor ranked #1 on power list of Analytical Scientists*

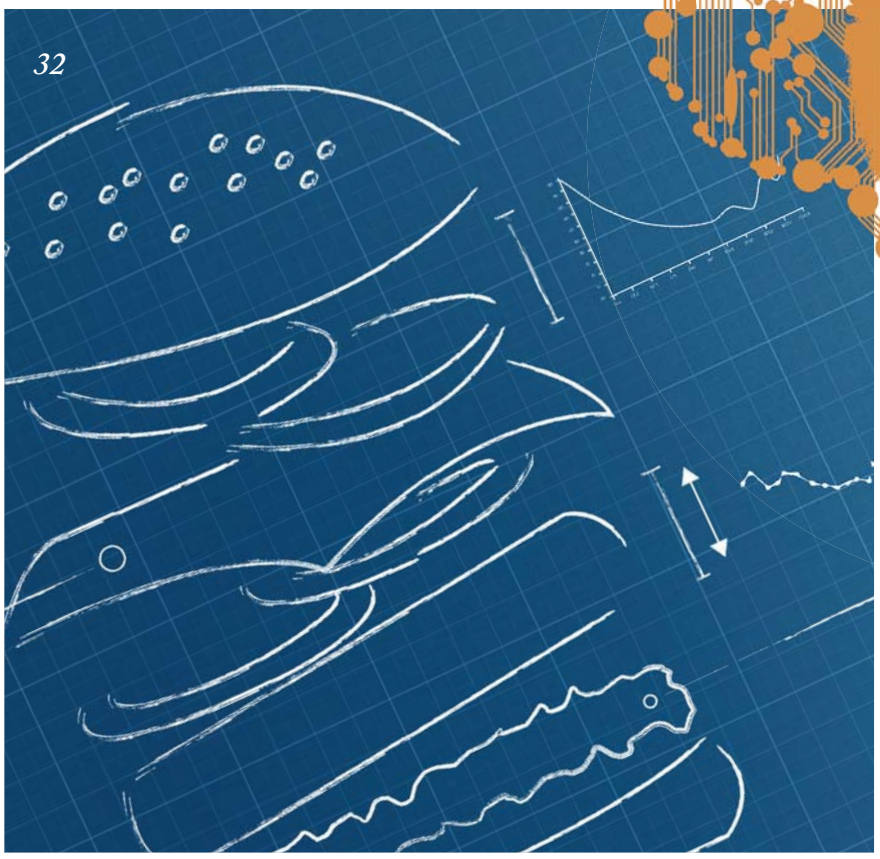
Oct 28 @908Devices: *Congrats to our Science Founder Prof Mike Ramsey featured in @tAnaSci Power List 2013 of top 100 influential people in analytical sciences*

Oct 26 @MSHeretic: *@tAnaSci Powerlist 2013 - do you agree?*

Oct 25 @AgilentChem: *Congrats to our own Bill Sullivan, Gerard Rozing, Monika Dittmann & Ron Majors for making the @tAnaSci Power List*

Thank you to all of our new followers. We're steadily gathering pace on Twitter but, as the saying goes, there is strength in numbers. To find out what's new, what's popular, what's on the horizon – or just to get in touch: @tAnaSci.

Contents



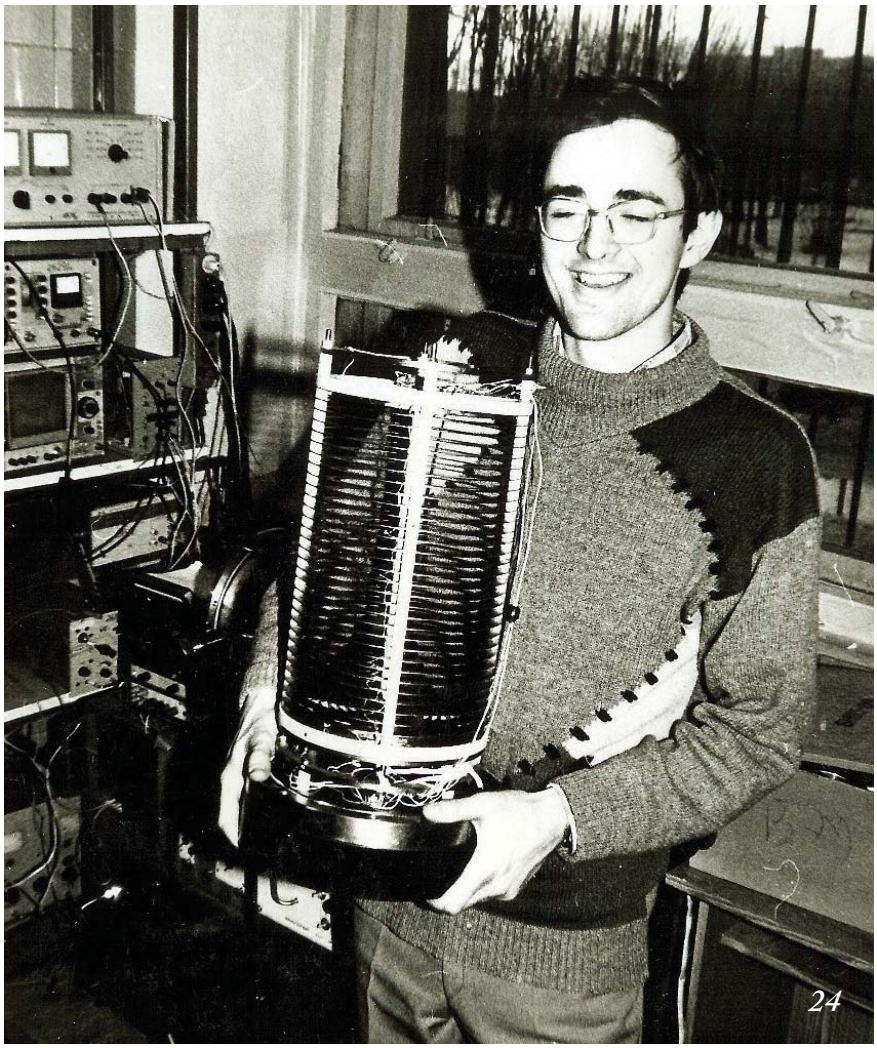
14

On The Cover

Alexander Makarov, inventor of the Orbitrap, past and present.

Upfront

In My View



Features

Departments

Sitting Down With

the **Analytical Scientist**

ISSUE 10 - NOVEMBER 2013

Published by
Texere Publishing Limited, Booths Hall, Booths Park, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK

General enquiries:
www.texerepublishing.com
info@texerepublishing.com
+44 (0) 1565 752883
sales@texerepublishing.com

Distribution:
The Analytical Scientist is distributed worldwide through 21,000 printed copies to a targeted European mailing list of industry professionals and 58,750 electronic copies, including 27,583 to North/South America, 26,509 to Europe, and 4,658 to the Rest of the World. ISSN 2051-4077

texere publishing ltd

J.T.Baker® chemicals: Optimized lab performance. Accurate results. No compromises.

Uncompromising Performance

J.T.Baker® chemicals are application-optimized and function-tested to maximize performance and the accuracy of your results. Reduce rework and improve throughput with J.T.Baker® brand products:

- High Purity Solvents
- Acids
- Salts
- Solutions
- Chromatography

Request a consultation or product sample

Let us show you how J.T.Baker® chemicals can improve your results. Contact us today at +31 (0)570 687500, **avantor.emea@avantormaterials.com** or visit **www.avantormaterials.com**

J.T.Baker®

Part of

AVANTOR™ PERFORMANCE MATERIALS

Women at the Top of Analytical Science

What can be done to improve on a disappointing show in The Power List?

One thing that stood out as we compiled the 2013 Power List was its paucity of women. Only eight of the 100, and none of the Top 20, were female. That's disturbing. Let's set 8 percent in context. Broad industry numbers are woeful: in the 2013 Fortune 500 list, which ranks the top US companies by gross revenue, women hold just 4.2 percent of CEO positions. This is mirrored in the European Union, where company presidents at 96 of the leading 100 businesses are male. A quick glance at the executive management of the leading companies in analytical science indicates that things are little, if at all, better there.

The picture in academia is brighter. Thirty-eight percent of faculty at US higher education institutions are female. However, there is a "pyramid problem". At the base, 50 percent of faculty at community colleges are women; this drops to 41 percent at baccalaureate and master's degree colleges and 33 percent at doctoral-level universities. Within the final category, the more prestigious universities hire fewer women still. It is a (qualitatively) similar picture in Europe; in Spain, for instance, 39 percent of associate professors are women, dropping to 18 percent for full professors.

Let's look at The Analytical Scientist's record. We have an Editorial Advisory Board of 15, three of whom are women (20 percent). In our first ten issues there were 140 authors and interviewees, of which 32 (23 percent) were female. Nothing to brag about – we need to take measures. However, given these numbers, one might have expected 20 women to be named in the Top 100. Why didn't that happen?

Perhaps it's because this aspect of the field is not yet mature. Sue Lunte (this month's "Sitting Down With" guest and one of the eight women on the Power List) mentions that when she was in grad school (not so very long ago), one in ten students was female while today it is one in two. As the increasing proportion of women work their way through the ranks, the numbers at the top of the pile will gradually increase. It may help explain why academia and this magazine's contributions from women stand at around 20 percent.

However, it is difficult to see how and when parity will be achieved. It is going to take a re-boot of the system, which was set up for men, by men. Perhaps simply changing "the message" is a good place to start: "We need to stop telling young women how hard it is to be a woman scientist and start telling them about how amazing the job is" - Professor Judith Mank, University College London (1).

Richard Gallagher
Editorial Director

Reference

1. *http://blogs.nature.com/soapboxscience/2012/07/13/toprecommendations-from-top-women-in-science*

John Coates

John Coates arrived in the USA from the UK some 35 years ago, with the goal of broadening his professional experiences and becoming more entrepreneurial. "In the late 1970s, the USA seemed to be the place to achieve professional growth, which was not easy to do in the UK," he says. Having gained experience in engineering, marketing and business development, he set up his own business in 1996, focusing on new technology and product development for instruments and sensors. "Today, one needs to work close to the edge to stay in business, but if you're comfortable on the edge then there are a lot of good opportunities and plenty of room for growth."

Get John's tips on setting up as a technology-based business consultant on page 44.

Imre Molnár

Before establishing the Molnár-Institute for applied chromatography in 1983, Imre Molnár completed his postdoc at Yale University under the guidance of Csaba Horváth, the developer of the fundamentals of modern chromatography. "He was a true scientist and a fascinating teacher, always available for discussions, and he had many students who loved him like their own father," says Imre. Together with Wayne Melander, they published the "Solvophobic Theory". After Yale, Imre began collaborating with Lloyd Snyder (see page 18) and John Dolan at LC Resources on the development of DryLab software, a tool for modeling complex separations in HPLC. Since 2006, Molnár-Institute has continued development in Berlin, Germany. Read Imre's views on QbD on page 24.

Konstantin Choikhet

Konstantin's interest in chemistry turned out to be a little stronger than his passion for physics and eventually took him to Heinz Engelhardt's group at the Institute for Instrumental and Environment Analysis of the University of the Saarland for his PhD. In 1999, he joined Hewlett Packard in Waldbronn, Germany as an R&D chemist. "Developing instruments for chromatographic and electrophoretic analysis is a field where I can extensively apply both my physical and my chemical side", he explains. "It helps to better understand strange or unexpected effects, if you observe them from different perspectives". Konstantin defends the volume-based HPLC on page 21.

Marc Bird

Marc Bird is a graphic designer with over ten years of professional experience. "My career began at London lifestyle magazine Dazed & Confused, and, after several years, I moved to Grand Designs Magazine – the accompaniment magazine to the TV series". After relocating to the North West, Marc continued working in design, for a classic music publisher and latterly for Live Nation producing marketing materials for their extensive theatre division. "More recently I set up a community interest company to provide creative support to third sector companies based in North West England," he says.

Marc's flair for design and eye for detail can be found on each and every page.

VWR We Enable Science

Hitachi High-Tech
HITACHI

IMPROVING PRODUCTIVITY IN HPLC ANALYSIS

1400 bar for new high resolution column technology

Very low system dwell volume

Tool-less column fitting

Superior resolution and sensitivity

ChromasterUltraRs

Continuing the tradition of manufacturing highly robust HPLC systems but now with additional novel new technologies; The ChromasterUltraRs effortlessly delivers a top class performance and the flexibility needed for today's laboratory.

Owing to the high pressure capabilities of the ChromasterUltraRs 250 mm or 300 mm UHPLC columns can be used. It is possible to couple two 3×250 mm 1,9 µm columns together in series in order to give the highest possible number of theoretical plates.

Band broadening is kept low owing to a low system delay volume of 120 µl (including one 55 µl mixer).

The novel double corkscrew mixer ensures excellent mixing with a very low composition ripple of 0,1 mAU. (Conditions: A H20 + 0,1% TFA, B: MeCN + 0,1% TFA, flowrate: 0,5 ml/min, A:B = 45:55 at 25 °C)

Need a demonstration? **Email: chromatography@eu.vwr.com**

For product information: **www.vwr.com**

Upfront

Reporting on research, personalities, policies and partnerships that are shaping analytical science.

We welcome information on interesting collaborations or research that has really caught your eye, in a good or bad way. Email:

rich.whitworth@texerepublishing.com

Like a Moth to the… Flower

The unique co-evolutionary relationships between plants and their pollinators are as complex as they are diverse. How can GC-MS analysis help?

Lead researcher Tomoko Okamoto and colleagues from Kyoto University, Japan, have analyzed floral scents from male and female flowers of the genera Phyllanthaceae to understand the behavior of female moths of the Epicephala genus (1). We caught up with her to find out more.

Why moths and flowers?

At the base of my interest lies the question, "How did flowers evolve and diversify?" The blooms of each plant species have unique traits – shapes, fragrances, colors – that guide pollinator insects to ensure its reproduction. The evolutionary process behind floral scents is less well understood.

When I was a university student, the mutualism between Phyllanthaceae and Epicephala was discovered by Makoto Kato. I was very surprised by the unique behavior of the female moth: she visits the male flower to collect pollen first, and then visits the female flower where she lays her eggs to secure food (from developing seeds) for her offspring. The moths visit only one host species, even if Phyllanthaceae plants of different species are growing side by side. And because they are nocturnal, it's all done in total darkness. I felt sure that Epicephala moths were unique in their advanced ability to process olfactory information, supporting the highly specific interaction and complicated behavior.

What did you want to prove?

In general, monoecious plants pollinated by animals exhibit very similar traits in the male and female flowers they bloom, because they want to be visited by the same pollinators to ensure fertilization. I wanted to provide the first example in which sexually dimorphic floral scent has evolved to signal an alternative reward.

Any surprises?

The volatile compounds emitted by male and female flowers of Epicephala-pollinated Phyllanthaceae plants are very different, often involving compounds derived from different biosynthetic pathways. For example, in Glochidion zeylanicum, male flowers emitted phenylacetaldehyde synthesized by a shikimic acid pathway, while female flowers emitted linalool synthesized by the MEP/DOXP pathway. Our results indicate that the pollination behavior of the Epicephala moth imposes very high selective pressure on sexual dimorphism of host plant floral scents, which surprised me.

How did you approach the challenge?

I collected floral scents form Epicephala pollinated and non-pollinated flowers using the headspace technique, and

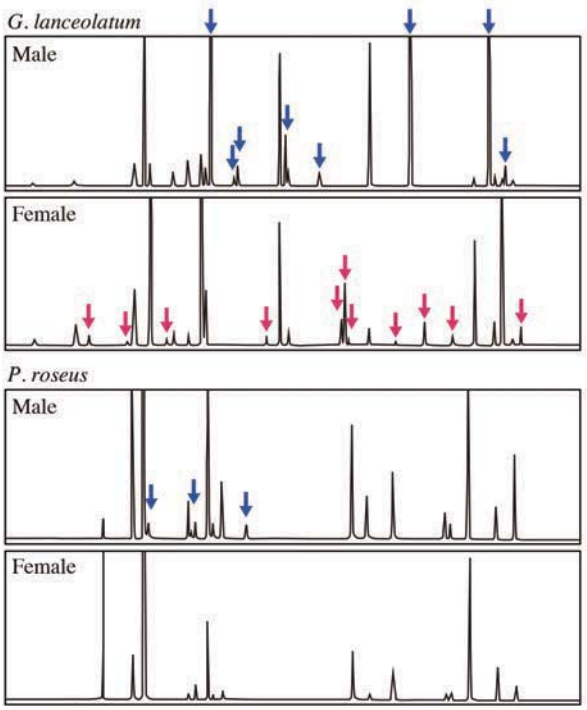


Figure 1. GC-MS total ion chromatogram of Glochidion lanceolatum (an Epicephala-pollinated species) and Phyllanthus roseus (a non-Epicephala pollinated species) floral scents, showing that a high proportion of the compounds are sex specific in Epicephala-pollinated plants. Blue and pink arrows indicate volatile compounds unique to male and female flowers, respectively.

analyzed them by gas chromatography–mass spectrometry (Shimadzu GC-MS QP2010) to create profiles of each floral scent. There were dramatic differences in floral scent profiles between sex in Epicephala-pollinated flowers, but no difference in non-Epicephala pollinated flowers (see Figure 1).

I also made a phylogenetic tree of Phyllanthaceae plants using previously published DNA sequences to check the evolutionary process of sexual dimorphism in floral scent. This revealed that Epicephala-pollinated plants evolved independently.

Finally, I conducted a behavioral test using Epicephala moths to check whether mated Epicephala moths with no experience of pollen collection are attracted by male flowers. I found that mated Epicephala moths do indeed prefer the male floral scent over the female one.

What next for your research?

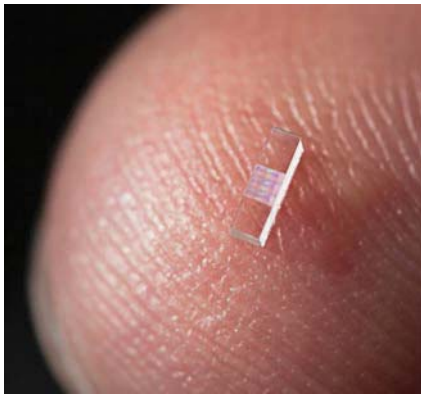
I want to try to understand how moths process complex olfactory information and how changes in scent volatiles lead to moths shifting to a new host, promoting speciation. *RW*

Reference:

1. *T. Okamoto et al., "Active pollination favours sexual dimorphism in floral scent", Proc. R. Soc. B 280:20132280 (2013).*

Nano Particle Accelerator

Is "accelerator-on-a-chip" technology the tipping point for cheaper, smaller devices for science and medicine?



Making "lab-on-a-chip" seem a tad pedestrian, researchers at the Stanford Linear Accelerator Center (SLAC) in California, USA, have developed a laser-driven dielectric microstructure – the size of a grain of rice – that can accelerate electrons at ten times the rate of the current SLAC linear accelerator: 300 million electronvolts per meter (1).

Mind-boggling physics aside, the system is beautifully simple (see Figure 1): near-lightspeed electrons from a conventional accelerator are focused into a 0.5 µm channel within a fused silica glass chip that is patterned with nanoscale ridges. The precisely-spaced ridges cause infrared laser light to generate electric fields that have the net effect of boosting electron energy.

"Our ultimate goal for this structure is one billion electronvolts per meter, and we're already one-third of the way in our first experiment," said Stanford professor Robert Byer, the principal investigator for this research, in a SLAC press release.

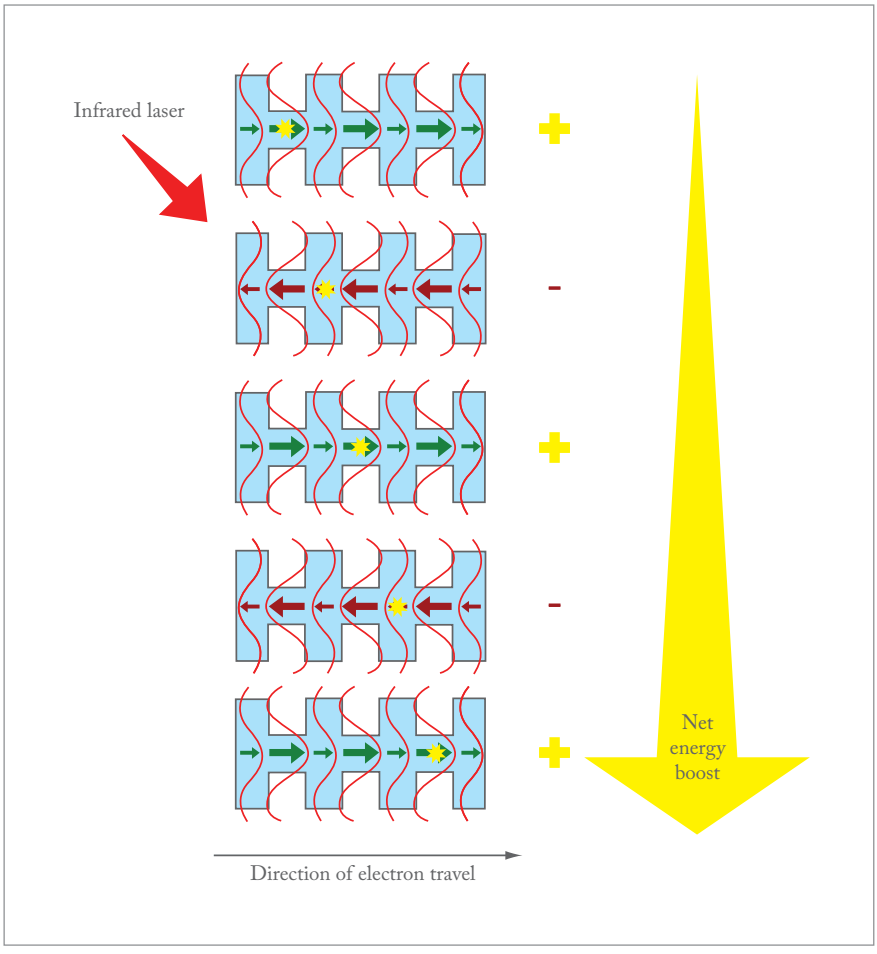


Figure 1. How the accelerator-on-a-chip works. The nanoscale pattern increases the laser light's electric field between the ridges and reduces it within the gaps. Electrons that are perfectly timed with the laser light wave receive a significant net energy gain as they pass through the channel. For video: tas.txp.to/1013/laser

Seeking more economical alternatives to conventional microwave-powered accelerators, Joel England, the SLAC physicist who led the experiments, admitted that there were a number of challenges that must be overcome before the technology is likely to be of benefit to the "outside world". Primarily, the need for a more compact way of accelerating electrons up to near-lightspeed before they enter the chip must be addressed. Still, with work, the team believe the technology will substantially reduce the size and cost of future high-energy particle colliders, and, said England, "It could also help enable compact accelerators and X-ray devices for security scanning, medical therapy and imaging, and research in biology and materials science." The term "tabletop accelerator" sounds most tantalizing. *RW*

What could you do with a tabletop accelerator? Let us know online: theanalyticalscientist.com/issues/1013/202

Reference

1. E. A. Peralta et al., "Demonstration of electron acceleration in a laser-driven dielectric microstructure", Nature, 27 Sept 2013 (10.1038/nature12664).

Sound Boost from Big Pharma

AstraZeneca joins forces with Labcyte to develop acoustic dispensing system for mass spectrometry

Labcyte's acoustic liquid handling system Echo aims to prevent errors that generate misleading results in drug development by using sound waves to dispense a wide variety of liquids in nanoliter increments (see figure 1). Now, AstraZeneca has proven its interest by collaborating on the development of an instrument that delivers test samples into a mass spectrometer. The hope? That it will generate better results at lower costs than traditional systems, which tend to suffer from transfer errors and sample contamination.

Figure 1: Acoustic energy is transmitted by a transducer through the bottom of a multi-welled reservoir and focused at the fluid meniscus. This causes a volumetrically precise droplet of fluid to be ejected from the source plate. The droplet is captured at the destination by surface tension. To transfer a larger volume, more droplets are transferred. Transfer of fluid is rapid with droplets being ejected as frequently as 500 times a second.

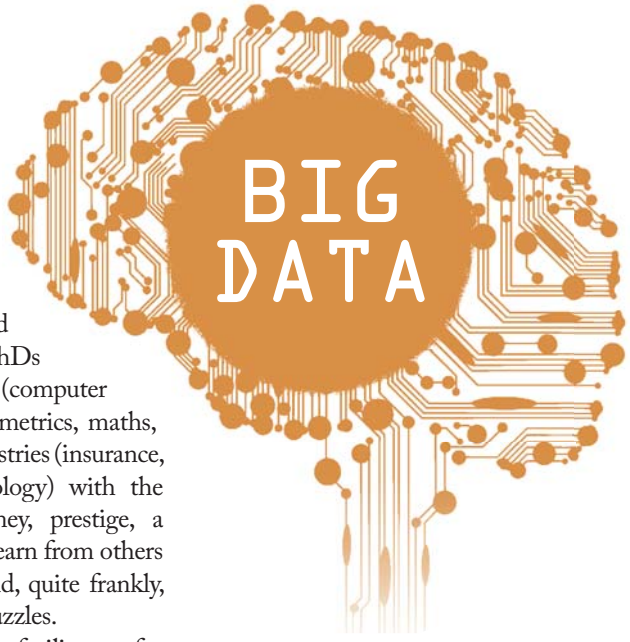
According to senior director Brad Nelson, "The goal of the project is to enable high speed acoustic loading of samples into a mass spectrometer, directly from an assay plate. This capability would enable direct detection of native analytes, without the use of surrogates, radioactivity, coupled assays, or indirect measurements. It would be a transformative capability for drug discovery".

Labcyte's system featured in the July issue of The Analytical Scientist (tas.txp.to/1013/acoustic) in an article that concluded that it did not wish to oversell the impact of the failure of serial dilutions in high-throughput screening (HTS) applications, but suggested there may be instances where researchers follow dead-end compounds in a doomed attempt to discover new drugs. A comment online disagreed only with the timid stance of the statement: "The last paragraph of this article is not an 'oversell' but rather fairly states the risk of continuing to use 'widespread and deeply entrenched' pipettes and serial dilution processes. For all the reasons given, not switching to acoustic direct dispensing seems unjustifiable."

Mike Snowden, AstraZeneca VP Discovery Sciences, said in a press release that it was two of their own scientists that discovered the potential benefits. He went on to say, "Combining acoustic delivery with mass spectrometry has the potential to open up new areas of science through transformational improvements in sampling rates and reductions in sampling volumes." *RW*

Data Scientists For Sale

Do you have big data, lots of questions, and no expertise? This crowd-sourced data analysis platform could be the answer – if you can afford it



What?

Kaggle is the world's largest community of data scientists, according to their own information. Within this gaggle of geeks, competitions are held to solve complex data problems, ranging from "Predict a biological response of molecules from their chemical properties" to "Dogs versus Cats". The latter sounds less serious, but demands the creation of an algorithm to distinguish images of the two mammals (something that's easy for humans, dogs and cats to do, but difficult for computers). The underlying intent is to test Asirra (Animal Species Image Recognition for Restricting Access) a form of CAPTCHA (Completely Automated Public Turing Test to Tell Computers and Humans Apart).

Kaggle is proud of its proven ability to solve "real-world problems" and the natural evolution is "Kaggle Connect", which is a nicer (and faster) way of saying "crowd-sourced data analysis consultancy".

Why?

Good data scientists are very much in demand – our August feature "Towards Tsunami Resistant Chemometrics" (tas.txp.to/1013/tsunami) gives an indication as to why. As 'big data' gets bigger and bigger, making sense of the binary prosperity is an increasingly common issue and commoditizing it might offer one solution. Kaggle is first out of the blocks and, with clients like NASA, Microsoft, GE, and Merck, it could well be on the right track.

How?

Kaggle has attracted tens of thousands of PhDs from quantitative fields (computer science, statistics, econometrics, maths, physics) and diverse industries (insurance, finance, science, technology) with the promise of prize money, prestige, a chance to network and learn from others of a similar mindset, and, quite frankly, extreme nerd-friendly puzzles.

The site acts as a facilitator for interactions between this elite group (who join the community for free) and those looking to solve a particular data problem. In the early days, it was simply a competition platform for public science competitions. With so much engaged talent (and quite possibly always part of the plan), Kaggle has sought to monetize the endeavour through Kaggle Connect, hiring out the elite of the elite (the top 0.5 percent of the community) as a consulting service.

Who?

The company was founded by CEO Anthony Goldbloom in 2010 in Melbourne, and moved to San Francisco a year later. In November 2011, Kaggle announced 'Series A' funding.

As for the users: data scientists can prove themselves in the competitions that appear on the site. Non-data scientists can learn about it on the company Wiki. And any company (presumably) can contact Kaggle to ask about the data analysis services available. *RW*

For more information or to add your brain to the cause, visit www.kaggle.com.

Thinking of testing Kaggle's platform with your own data analysis issues? Let us know: rich.whitworth@texerepublishing.com

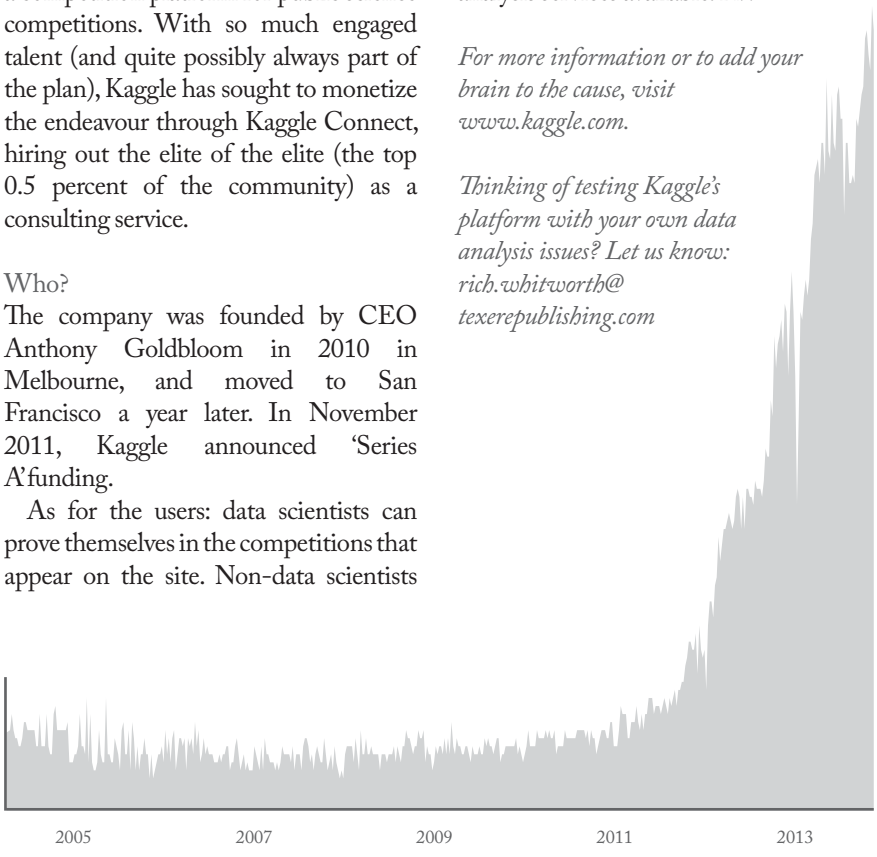


Figure 1. Search interest in "Big Data" over time (source: Google Trends)

Evaluate & Explore

ANALYTICAL CHEMISTRY AT PITTCON 2014

PITTCON™ CONFERENCE & EXPO 2014

March 2-6, 2014
Chicago, Illinois
www.pittcon.org

Pittcon is the leading conference and exposition for the latest advances in Analytical Chemistry. Attending Pittcon gives you a unique opportunity to get a hands-on look at cutting-edge product innovations from leading companies. Participate in the Technical Program to learn about industry trends and discover new applications and methodologies used in analytical chemistry. Topics include the latest in spectroscopy, mass spectrometry, separation, microscopy, and more.

For more information on technical sessions, exhibitors and short courses, visit **www.pittcon.org**.

Follow Us for special announcements

Fame and Fortune?

Having thrust 100 analytical scientists to the heights of stardom in our 2013 Power List, we went back to assess the reaction of colleagues, friends and family. The response was mixed.

"A very typical response. People in my own group reacted and I got email messages from people around the world. The people in between have remained remarkably quiet. Does recognition as a function of distance follow a van-Deemter curve (see Figure 1)? This may be generally true. Who is ever appreciated by middle management (except middle management)? Or is the range in the middle immune to information, even when presented nicely?" – Peter Schoenmakers (Number 7).

"It has been a crazy week. Your list attracted a lot of attention at least at our institution. I got a lot of emails about it, and mentions on LinkedIn and I heard from people that I haven't been in touch with for a long time. It's been interesting. I was surprised and honored to be on the list." - Sue Lunte

"A colleague of mine saw the list and mentioned that he was pleased to see me in it. Such rankings might sometimes include embarrassing omissions; therefore, I tend not to take them too seriously. Thanks for including me despite the fact that I don't know exactly how I made it to the list!" - Christian Griesinger.

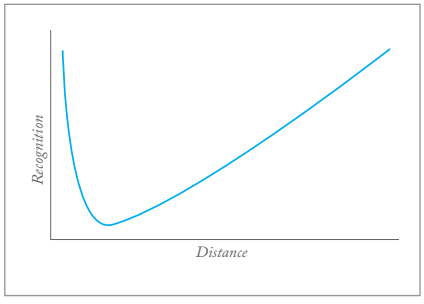


Figure 1. Recognition as a function of distance: reactions to the Power List.

My colleagues in the Netherlands noticed it and congratulated me. To show that I really approve of it, I also uploaded it on our website! - Lutgarde Buydens

Other Power Listers made "the headlines":

- Eccellenze Unime: Il Prof. Mondello Nella Analytical Scientist Power List (tas.txp.to/1013/power1)
- Richland Scientist Recognized for Work on Biological systems (tas.txp.to/1013/power2)
- Phenomenex CEO, Fasha (Farshad) Mahjoor, Named Top 100 Most Influential People in Analytical Sciences (tas.txp.to/1013/power3)
- UniMe. Il prof. Mondello tra i 100 più influenti in Scienze Analitiche (tas.txp.to/1013/power4)

Lloyd Snyder delves more deeply into what a pecking order actually means on page 18.

Soybean Blunder

Taiwan proudly set the tightest limits on glyphosate, but failed to measure the herbicide.

Regulatory officials have been rapped on the knuckles by Taiwanese legislator Lin Shu-fen for an oversight in the regulation of glyphosate residues in soybeans, according to the Taipei Times (1).

Lin noted that, "Taiwan has a maximum residue limit (MRL) for glyphosate of 10 parts per million (ppm), which is lower than that of the US, Japan and the Codex Alimentarius at 20ppm." So far, so good. "However, the problem," Lin continued, "is that what we have been using for testing is the 'multi-residue analysis,' which analyzes the residue levels of 251 pesticides at one time, and glyphosate is not one of them." Given that Taiwan imports some 2.4 million tonnes of the legumes – 99.95 percent of all soybeans used – this is no small oversight.

Glyphosate is one of the world's most commonly-used broad-spectrum herbicides. In terms of safety, according to an US Environmental Protection Agency (EPA) factsheet, it poses little threat: "EPA conducted a dietary risk assessment for glyphosate based on a worst-case risk scenario, that is, assuming that 100 percent of all possible commodities/acreage were treated, and assuming that tolerance-level residues remained in/on all treated commodities," and concluded that the chronic dietary risk was minimal (2). Unfortunately, the safety of glyphosate at the MRL becomes irrelevant when it is not being monitored at all.

Following Lin's accusation, Wu Hsiu-ying, deputy chief of Taiwan's Food and Drug Administration (FDA), and Tsai Shu-jen, chief of the FDA's food division, promised that imported soybeans would be tested for glyphosate residues with immediate effect (3).

Back on track then. But are there any other impressive residue-limits that are applied without adequate analyses to back them up? That's an interesting question.

Experts sit around the table to discuss food safety on page 34.

References

1. tas.txp.to/1013/soybean

2. www.epa.gov/oppsrrd1/REDs/factsheets/0178fact.

3. focustaiwan.tw/news/asoc/201310280033.aspx

In My View

In this opinion section, experts from across the world share a single strongly-held view or key idea.

Submissions are welcome. Articles should be short, focused, personal and passionate, and may deal with any aspect of analytical science. They can be up to 600 words in length and written in the first person.

Contact the editors at edit@texerepublishing.com

Who's on Top?

Is there a pecking order for scientists? If so, how is it determined and what does it mean?

By Lloyd Snyder, now retired and living in Orinda, California, USA.

Interpersonal comparisons are seldom far from view, whether pursued on Facebook by teenagers, employees climbing the corporate ladder, or magazines profiling some "Top 100" or other, as this publication did last month. Indeed, scientists may represent a prime example. A former boss of mine was a physicist and insisted that physics was the preeminent science. After all, once you really mastered physics, you should be able to understand all the other sciences… or so he said. So, physicists were on top, presumably followed by members of other "hard" sciences, such as chemistry and geology, then the biological sciences, and finally social sciences at the bottom: a well-defined pecking order.

Pecking orders in science can be defined in other ways too; for example, scientists in industry versus academia, or those working in research versus in those in development. Industrial scientists tend to be associated with development, and academic scientists with research. Here, I will set aside these and other distinctions between groups of scientists.

Followers, Awards and Facilitation

How do scientists compare each other? There are some widely used measures of recognition, including who has the most followers, who receives the most awards and who best "facilitates" the research of others. Let's look at these in turn.

By "followers" I mean fellow scientists around the world who follow one's work. Results can be disseminated in presentations at meetings, or in publications via papers, review articles and books. Transient recognition can be achieved by a single presentation at the "right" meeting, but a proper ranking of individuals usually takes more time.

Advanced placement in a science hierarchy usually requires an extended period of productivity; publications and citations can together provide an initial assessment. As a single "productivity parameter", the h-index is often used; it represents the number n of papers that have been cited at least n times. If your 20 highest cited papers have each been cited at least 20 times, your h-index is 20. A higher number naturally commands more respect. The quality of the journals in which an author publishes is also a factor, but the h-index recognizes this indirectly; publications in lesser journals are less likely to be highly cited. Authoring a review or book provides a complementary form of recognition, but mainly to the extent that such publications highlight the author's own research. A review or book that does not do this may still be a valuable contribution, but this will be recognized somewhat differently than one that showcases the R&D achievements of the author. That is, achievements in teaching and R&D are usually recognized separately.

Are awards the ultimate measure of performance and pecking order? Yes and no. First, such recognitions vary greatly in significance. There are the Nobel prizes at the top, and employee-of-the-month awards at the bottom; collecting many "minor"

"Are awards the ultimate measure of performance and pecking order? Yes and no."

awards does not add up to a major one. Second, to receive an award, someone must nominate you. Many deserving awardees are never nominated, or are only nominated years after less deserving candidates receive a particular award. Third, important contributions may be made by workers who lack self-assertion, or the "image" associated with advanced degrees, high-ranking mentors, or chaired professorships from prestigious universities. Their work may linger in obscurity, or even be attributed to someone else. Lastly, favoritism and self-promotion can play significant roles in the award and honors selection process, just as in climbing the corporate ladder.

What about those who facilitate the research of others? This includes members of granting institutions, organizers of meetings, and editors of journals. Each of these activities can contribute directly to the advance of science. In addition, people who have money to support work by others enjoy the power of the purse, not an insignificant factor in commanding respect. Similarly, those who head scientific meetings receive additional status because of their ability to invite and support speakers. Editors of journals are also noted for their role in accepting some papers for publication, and rejecting others. Many other people also facilitate the work of those around them, often in more significant ways. Some of these are mentioned later in this article.

Societal Contribution

But what counts as "real" achievement? Publications, awards and research facilitation are at best indirect measures of scientific "success", and are often more relevant to workers in academia than to workers in industry. We would all like to believe that "real" respect comes as a result of our contributions to society through the development of new ideas, information, or products. The relative value of such achievements is determined by how much they advance a particular area of science, and in turn how much this contributes to human welfare. An accurate assessment of people in this way may require more effort than just adding up publications, awards, and so on.

In order to better visualize the nature of such "real" contributions, let's consider high-performance liquid chromatography (HPLC), which over the past 50 years has been widely recognized as a major contributor to advances in chemistry and biochemistry. More specifically, let's focus on columns for HPLC; advances in HPLC since the mid 1960s have been closely tied to corresponding improvements in the column. At the onset of HPLC, the theory of column performance was well understood in general terms, as a result of the prior contributions of several workers. But actual columns at this time fell far short of what later proved possible.

Over the next five decades, the further development of column theory became a cottage industry, yet these added insights have played a relatively minor role in the actual preparation of better columns. Columns mainly improved as a result of successive advances in the laboratory, including:

- Procedures for the direct synthesis of small, uniformly sized particles, as opposed to size

"Present fads in R&D will be replaced by others as time passes, leading to changes in the current ranking of scientist"

classification methods
- Successive improvements in the way small particles are packed into the column
- The use of highly-pure silica particles
- The development of more stable and reproducible bonded phases, especially for use in reversed-phase chromatography
- The preparation of so-called "superficially porous" or "fused-core" particles

While several names are now associated with present-day column theory, one name stands out for corresponding practical improvements of the column. This person pioneered each of the above five laboratory advances, and for the past 50 years he has been a major factor in making HPLC the valuable tool it is today. It is clear that Jack Kirkland deserves "real" respect. The widespread use of his columns, with all of their related benefits, more accurately describes Jack's contributions to science than his impressive list of publications, patents, awards and other honors.

Some Final Caveats

Recognition can be both fleeting and somewhat superficial. Present fads in R&D will be replaced by others as time passes, leading to changes in the current ranking of scientists. Remember "polywater" in the 1960s? Or "cold fusion" in the late 1980s? Or more recently _____ (fill in your own choice)? Even less-ephemeral research areas, such as HPLC undergo major changes in emphasis over time, with new "hot" topics emerging and old ones fading into obscurity (however, this has not been the case for HPLC columns!).

Credit among scientists is often determined by who got there first. However, today's discoveries seldom occur in a vacuum, while not infrequently different R&D groups arrive at the same place at a similar time. Small differences in timing may be critical for the patent system or the Nobel committee, but more important than "Who was first?" may be "Who did it best?"

Similarly, a single name is often associated with a specific scientific advance. More commonly, however, that person has had important help from co-workers or collaborators, as well as earlier guidance by teachers and mentors. These contributors are seldom remembered or appreciated, except by those directly familiar with their efforts and essential skills.

Finally, we should keep in mind that human progress depends on the totality of achievements by many different workers, none of whom were truly essential, not even Newton or Einstein. Truly, the sum is greater than its parts, and everyone who contributes is important in some degree. On the other hand, while "key" individuals may be non-essential over the course of a century, they can make a huge difference over shorter periods of time.

So, recognition and ranking can be both ephemeral and overrated. Does the pecking order then represent a useful way of assessing the people around you, a misleading distraction, or something in between?

You decide. ■

Debating Volume-Based HPLC

An article by Monika Dittmann on volume-based HPLC (tas.txp.to/1013/volumeLC) triggered a debate on the practicality of the concept. Here, we present the questions that were raised and how they were answered.

Volume-Based HPLC Isn't Practical

Posted online by "Chris" an R&D Director/Manager in the USA

In real life [volume-based HPLC] couldn't work. Since a column invariably increases in pressure with use, the constant pressure mode will translate to drifting flow-rate mode.

Imagine for example, that you have a column operating at 7000 psi at the beginning of a gradient separation. In this example, let's say that the column flow rate at the start of the separation was 1 ml per minute. Now, imagine that, after injecting real samples for a week, the flow rate at the beginning of the separation drops to 0.9 ml per minute when the pressure is set at 7000 psi, due to the accumulation of particulate at the head of the column from the samples

"I think it's extremely unlikely that any instrument manufacturer would undertake such an effort"

injected. Surely there's a problem when the flow rate has significantly changed from the conditions originally used the week prior? If one were to stick with constant pressure mode, the flow rate would be slowly dropping over time as long as the pressure is held constant. To put it another way, when we operate at constant flow rate we are used to seeing the pressure increase slowly over time on a given column, so if we choose to operate at constant pressure we can expect to see the flow rate slowly decrease over time. The difference is that nothing significant changes about the analytical method when we work at constant flow rate but the method will be significantly different in terms of speed as the flow rate slowly drops. This is the issue that concerns me about this proposed mode.

Even if there were good tools for converting an elution time plot into a volume-based plot, which would partially obscure the issue, it doesn't address the underlying issue of gradually decreasing flow rate over time as the pressure on the head of the column increases with use. Because the actual analysis time is flow rate dependent in the constant pressure mode this would mean that the analysis time would be continuously increasing over the life of the column. This would have two significant impacts: (1) the analysis time would be significantly increased, decreasing sample throughput, and (2) the chromatographic efficiency of the separation would change over time, changing resolution and in some cases even elution order, since elution order can be mobile phase composition dependent.

Because gradient programs are time-based not volume-based (unless you change that to a volume-based program too) there would be issues with reproducing gradient chromatography over time. I guess it's possible that instrument manufactures might choose to implement such a tool, but it's hard to see why they would try to do so unless they had an online flow meter to enable accurate plotting of the chromatogram on a volumetric basis. While it is true that one could theoretically get away with a time-to-volume conversion without a flow rate measurement, the accuracy of such an approach is questionable. Frankly, I think it's extremely unlikely that any instrument manufacturer would undertake such an effort for such a minimal benefit. Furthermore, it's hard to imagine that anyone would consider this as a viable option in a real analytical lab. ■

Volume-based HPLC Works

Konstantin Choikhet, Research and Development Chemist at Agilent Technologies, Boeblingen, Germany, and one of the inventors of Volume-based HPLC, responds.

Chris' comment gave me pause to

stop and think about how volume-based chromatography is perceived in the field. Here, I discuss the concept, how it could look and feel for a user, and what constraints and benefits one could face using these approaches.

As discussed in a number of publications and conference presentations that have referenced "constant pressure" or "volume-based" chromatography (1-3), the essential parameter that governs retention in chromatography is the volume of mobile phase passed through the column. Time-based description of a chromatographic process (although widely used) is in fact a special case, which is only adequately applicable if the flow rate is constant. Although this is convenient for a number of reasons, it also causes significant limitations.

It has been shown that chromatographically-consistent results can also be obtained without strict control over the flow rate (2, 3, 5). If the eluent composition plotted against delivered volume (the gradient program) remains unchanged, the plot of the detector signal versus delivered volume (the chromatographic output) will also stay essentially unchanged, nearly independent of how the flow rate was changing during the separation.

First, a few definitions: "Volume-Based (VB) LC" means executing a gradient program in accordance to the delivered volume (rather than to elapsed time) and handling the chromatographic output over an X-axis representing eluent volume. "Constant Pressure mode" is a special implementation of the VB approach. In this mode the pump keeps system pressure constant by continuously adjusting the flow rate. As with any innovation that changes established processes, the VB approach faces certain reservations from potential users. I will assess how justified those reservations are by answering a number of frequently asked questions.

"Volume-based mode is not a replacement, but is rather an add-on to the common operational modes."

Do I need to change my methods?

VB mode is not a replacement, but is rather an add-on to the common operational modes. An instrument capable of VB operation can also be used in constant flow regime but gives the user the option to run an existing method in constant pressure mode. Furthermore, VB-operation might not even be perceived as a method change by the majority of users. For example, your conventional method with its flow rate and composition time-table are displayed, but now an additional parameter called "execution pressure" and a checkbox "optimized throughput" are available. You set the execution pressure as you like, say 1150 bar, and tick the checkbox. That's it! The instrument will take care of the rest.

What are the benefits?

The benefits of using constant pressure mode are the elimination of overpressure shutdowns (you have defined an execution pressure that will be actively maintained and thus never exceeded), throughput increase by 10-25 percent due to the more efficient use of the available power range, also the column stress is lowered by eliminating gradient pressure cycles.

What would my chromatogram look like?

"An instrument capable of volume-based operation can also be used in constant flow regime"

You could let it be plotted with milliliters at the X-axis, if you like. But you might also want to make it look more familiar, in which case, the evaluation software would convert the volume X-axis to a time X-axis corresponding to the flow rate of your original method. The chromatogram would then match the one you got running your method conventionally. Not only is there similar reproducibility between modes, but also an excellent coincidence of retention volumes and peak areas (3).

Is the transition to VB operation entirely seamless?

Not exactly. There would still be some differences to the conventional constant flow method execution, which should be taken into consideration. These differences are:

- If any action outside the instrument needs to be synchronized to certain phases of a separation (a possible situation in multi-vendor systems with only rudimentary communication between system parts), the transition might be challenging, because the duration of every single separation and separation phase might vary depending, for example, on variations in system permeability.
- Due to flow rate changes, the efficiency for some peaks might be

increased or decreased compared to the constant flow mode, depending on where your original separation was on the van-Deemter curve.
- As already understood from method transfer from HPLC to UHPLC, selectivity changes could occur for substances with strongly pressure-dependent retention coefficients (4).

And what about quantitation?

If the detector you use is composition-sensitive (for example, UV or fluorescence) the converted chromatogram can be integrated exactly as the one run with the original method and the integration result will be essentially the same. Quantitation with mass-sensitive detectors (optimized LC-MS interfaces under certain conditions) is also straightforward. Detectors that are not purely concentration- or mass-sensitive are more challenging; that discussion exceeds the scope of this commentary but has been covered in the literature (5).

Will the approach be broadly accepted?

We will see if the VB approach finds its way into a broad user community, but it seems attractive enough to give it a try. ■

References

1. *K. Broeckhoven et al., "Kinetic performance limits of constant pressure versus constant flow rate gradient elution separations. Part I: Theory", J. Chromatogr., 1218, 1153–1169 (2011).*
2. *M. Verstraeten et al., "Kinetic performance limits of constant pressure versus constant flow rate gradient elution separations. Part II: Experimental", J. Chromatogr., 1218, 1170–1184 (2011).*
3. *M. Verstraeten et al., "Comparison of the quantitative performance of constant pressure versus constant flow rate gradient elution separations using concentration-sensitive detectors", J. Chromatogr., 1232, 65–76 (2012).*
4. *M. Fallas et al., "Influence of phase type and solute structure on changes in retention with pressure in reversed-phase high performance liquid chromatography", J. Chromatogr., 1297, 37–45 (2013).*
5. *M. Verstraeten et al., "Quantification aspects of constant pressure (ultra) high pressure liquid chromatography using mass-sensitive detectors with a nebulizing interface", J. Chromatogr., 1274, 118–128 (2013).*

Pharmacopoeias Need QbD

Incorporating updated analytical methods and approaches into pharmacopoeias – the bibles of pharmaceutical standards – would save a great deal of time and money.

By Imre Molnar, Institute for Applied Chromatography, Berlin, Germany

Despite all our knowledge and investment, drugs are available to treat only 20,000 of the 100,000 human diseases that have been described. On top of this, nine out of every ten drug development projects fail. I have a modest suggestion for improving these numbers.

Between 1970 and 2000, high performance liquid chromatography (HPLC) in the reversed-phase mode was the key analytical technique for safe drug development and production (1). As methods in this period were often unreliable, regulatory authorities applied pressure on companies to produce thorough drug master files (DMFs), detailed documents that contain the chemistry, manufacturing and controls of a drug component. A producer of an active pharmaceutical ingredient (API) describes in a DMF the intended methods of Quality Control, often with reference to the relevant pharmacopeia – the national and international standards that aim to harmonize quality specifications for selected pharmaceutical products, excipients and dosage forms. Any changes to DMFs were studied very rigorously with the handling of "Out of Specification" (OOS) data being especially tedious and time-consuming. While computer-supported techniques allowed a shift from trial-and-error toward a more systematic design of experiments (DoE), events like the Thalidomide disaster forced regulatory authorities to remain very strict.

In 2002, the pharmaceutical industry submitted a protest note to the US Food and Drug Administration (FDA) requesting more flexibility in the treatment of changes to analytical HPLC methods. The FDA reacted positively to this, introducing Quality by Design (QbD) as a replacement for "quality by QC" or "quality after design". QbD represented a paradigm shift; it holds that quality should be built into a product through the understanding of that product and the processes by which it is developed and manufactured. Knowledge of risks in the manufacturing and analytical processes, and how to mitigate these, are incorporated into QbD development.

"The QbD initiative changed the process of pharmaceutical production considerably."

The QbD initiative changed the process of pharmaceutical production considerably – and the working lives of people responsible for quality control. Today, methods can be planned in advance within a "design space" so that changes in conditions will not require new validation. A Control Strategy allows for a reexamination of working points at regular intervals and without regulatory interference.

However, there is some reluctance to introduce new methods because of the strong influence of pharmacopoeias. New methods come with high validation costs. Unfortunately, many pharmacopoeia methods are outdated and suffer particularly from long analysis times. In such cases, the application of QbD principles would greatly increase the flexibility of the analytical procedures required.

When a colleague submitted several DMFs to a number of European authorities they were approved, but only with the note "satisfactory". Later, he had a case in which the pharmacopoeia method took 160 minutes analysis time (2). The drug needed only one day in production, but it took, according to the old pharmacopoeia method, five days to be analyzed. As the colleague reworked the method using modeling software, he was able to reduce the analysis time down to three minutes. Upon submission, the DMF was approved very quickly by the regulatory agencies, with the note "excellent". The QbD-based process explains and proves why the final method, based on solid science, is the best one.

There are many similar opportunities. Modeling with software tools that follow QbD principles can help reduce the barriers to acceptance by regulatory agencies and play a part in increasing the speed of new drug development. And those suffering from the 80,000 diseases we cannot treat could certainly use the help. ■

References

1. *Cs. Horváth, W. Melander, and I. Molnár, J. Chromatogr. 125, 129–156 (1976).*
2. *A. Schmidt and I. Molnár, J. Pharm. Biomed. Anal., 78–79, 65–74 (2013).*

Super Clean™ Gas Filters

with Electronic Indicator

new

'Talking' Filters!

Fast Stabilization
Helium Filled GC/MS Triple Filter

Traditional Indicators
Uses sensitive color changing indicators to identify leaks or other system failures which can cause pre-mature saturation

Compatibility
New **Universal** Ring Nut. Easier Installation and improved compatibility with other base plate systems

Electronic Indicator
Progressively displays real-time filter status instead of a 'last minute' color change from traditional indicators, allowing you to determine a more controlled replacement schedule for your installation to prevent unexpected downtime

New Universal Ring Nut

- Serves as a **mounting point** for the Electronic Indicator device
- Easier attachment of genuine SGT purifiers to **competing** base plate systems.
- Can be used to **retrofit** (competing) filters with an electronic indicator
- **Backwards** compatible

Electronic Indicator

- Audio-visual **early warning** system
- Enjoy **additional replacement filter discounts** when filter is replaced according schedule
- Can be **linked** to our virtual indicator platform or can be **manually** configured according your replacement schedule preferences.

www.virtualindicator.com/preorder

For more information go to www.virtualindicator.com - Pre-ordered items are targeted to be shipped November 2013

Orbitrap Against All Odds

The development of Orbitrap™ has taken up all of my professional life. It's been a story of luck, perseverance, occasional deep insight and, ultimately, success. But for me, the implementation of Orbitrap has only just begun. Here's how we did it, and where it goes from here.

By Alexander Makarov

One dark day in the autumn of 1999:

Thermo's research elite arrived for a demonstration of the Orbitrap. *I switched the instrument on, only to discover that the turbopump was dead – a rare event, and difficult to repair. The delegation was scheduled to leave at noon the next day, so time was of the essence. I ran over to Thermo Masslab, shouting, "Please, please, give me a pump." They had one that I could substitute for ours, which was a stroke of luck. I ran back to the lab and used the night hours to install the new pump and put the instrument back together.*

I arrived at the lab early the next day to make some final preparations. To my despair, I discovered an electrical short inside the vacuum. I couldn't break the vacuum because there would be no chance of measuring anything at all. This, for me, is the lowest point of the entire story.

The instrument was too big to be picked up, so I started to shake the chamber containing the Orbitrap analyzer – far from recommended behavior when dealing with turbopumps. Yet, somehow, the shorted wires inside the vacuum moved away from each other and the system started to operate. When the delegation arrived, they witnessed high resolution and high mass accuracy. All in all it was very lucky and, in hindsight, rather fun; but it was also very bad practice – people get sacked for doing that sort of thing.

That was just two days from the many years that I've spent developing Orbitrap but it encapsulates the whole story. We knew from the outset that it wouldn't be easy but had hoped that once we climbed the first "mountain" everything would get more straightforward; however, what we found when we reached that first summit was a whole range of higher mountains stretching one after the other into the distance. Year by year, one by one, we conquered them. Only later did we think about just how close we were to falling off the cliff face: many times we were hanging by a thread but, possibly because we were moving so quickly, we didn't get easily discouraged.

But let's go back to the beginning…

Small company, big ambitions

I set out with very little knowledge – just optimism based on the absence of negative information. The seed of motivation was sown in my early days at HD Technologies in Manchester, UK, which I joined officially in 1996. As a start-up, HD was fighting just to ensure survival and yet we were very ambitious, convinced that this small company could contribute something significant. Everything was still relatively new to me: I only arrived in the UK from the former Soviet Union with my family in August 1994. HD Technologies greeted me with a distinct air of excitement and creative freedom. We had so many ideas that we could implement and realized that we needed something that was thoroughly unusual, something that no other company could develop. When I told him of my dreams, Steve Davis, the head of the company, said to me, "Alexander, it needs to be the ideal mass spectrometer, with the resolution of Fourier transform ion cyclotron resonance (FT ICR), the sensitivity of linear time-of-flight (TOF) and the size and capabilities of a quadrupole ion trap."

I knew Steve from the early nineties when he was working at Kratos Analytical (now Shimadzu), also in Manchester. He was the manager of MALDI TOF and they had just released the Compact MALDI III instrument. Steve had big plans and urgently needed someone with ion-optical experience. At the time, I was just traveling around after my PhD. Because I didn't have any money, I would arrange with universities to give a lecture and they would pay for my stay and train ticket to the next venue. One of the presentations was at the University of Salford and, although Steve wasn't there, his colleagues were; thinking that I sounded like an instrumentation guy, they suggested that I talk to their manager. I was still in the UK when Steve returned from Australia. Our meeting must have gone pretty well because he asked me to become a consultant for Kratos. Unfortunately, however, Shimadzu reorganized Kratos

and, instead of hiring me, shut down all magnetic sectors (indeed, they temporarily stopped all R&D projects in favor of production support).

This turn of events pushed Andy Hoffman, who worked on the electronics side, and Steve Davis to make an important decision. They used a request for voluntary redundancy to resign, received redundancy money, and set up their own company – HD Technologies. For the first two years, they didn't have the money to hire me, but they helped me to get a postdoc position. During that time, we often met together, discussing plans, and finally they managed to secure sufficient contracts to get me on board. The deal was that from 9am to 5pm (actually, it was more like 9am to 9pm) we would focus on contract projects, but that we would use our weekends to work on something "out of the box". I guess it was the kind of creative, progressive atmosphere that is typical of small companies that succeed; yes, we needed to find money for the next month but, at the same time, we knew that we needed to do something unusual to break that vicious cycle. Soon I started talking about an idea I'd had that used my knowledge of TOF technology.

I have to admit that 20 years ago I didn't know anything about running instruments properly; my PhD was mainly theoretical but the interaction with the Kratos Analytical team taught me that, if I stayed that way, there was little room for me in the lab. I started out pretending that I knew what I was doing but I learned quickly. Working with my hands at HD Technologies gave me a practical understanding of real-life problems, and it was while doing this that my ideas about a new mass spectrometer started to turn into something more concrete.

A typical conversation would have me proudly announcing to my colleagues, "Look! I have a trap – we just need to inject ions, but basically it's done!," followed by their skeptical cross-examination about how the ions would get inside. "What? Isn't it clear?" I would ask. After explaining in more detail, they might or might not agree (in actual fact, getting ions into the trap is more complicated than analyzing them once they are there). I listened to every query and challenge, went away to think about them, and then came back with another idea. Then they'd laugh and tell me I hadn't thought about another aspect – pumping, for example. We went back and forth this way, with me accumulating a thick stack of papers filled with formulae and calculations. In hindsight, despite the tough time that they gave me, my colleagues were too optimistic: reality would be much tougher. Nevertheless, these early calculations were enough to win a UK Smart (Small Firms' Merit Award for Research and Technology) grant. It was only about £50,000 but it allowed us to make a start and, perhaps more importantly, it set a fixed deadline to deliver something. The project was assigned development time, allowing me to work harder on it. If this had not happened we would have probably been consumed by the everyday, routine contracts.

ASMS Game-changer

When we started to design the instrument there were further clashes between theory and reality, requiring us to adapt to all kinds of problems on the fly. In fact, we didn't bother to test the first prototype because by the time the design was finished

1923
K. H. Kingdon proposes the principle for orbital trapping.

1953
M. I. Korsunskli and V. A. Bazakutsa publish a study of the ion-optical properties of a sector-shaped electrostatic field.

1981
R. D. Knight publishes on storage of ions from laser-produced plasmas.

Early-1990s
Alexander Makarov tours the UK's universities and meets Steve Davis of Kratos Analytical.

1996–1998
Alexander joins start-up HD Technologies, founded by Steve Davis and Andy Hoffman, and is tasked with delivering a new high resolution, accurate mass MS system; he proposes orbital trapping. HD Technologies wins a "Smart" grant to the tune of £45,000 from the UK government.

and the parts were made, it was clear that we didn't have the right electronics for it. I lacked electronics experience and designed a very simple solution but it is still used today to drive the central electrode, so it turned out to be very robust!

Our perseverance eventually yielded a working experimental set-up. Creating ions was easy because of our MALDI TOF experience using lasers, and when you have pulse packets it's easier to capture the ions in the trap. We obtained our first spectra in October 1998. The system produced increasingly high resolution, reaching 150,000 by July 1999, at which point we presented our proof-of-principle at the American Society for Mass Spectrometry (ASMS) meeting in Dallas, Texas. They were pretty simple data from unreliable and unstable equipment, but they showed off the unmistakably high resolving power of the "Orbitrap" (see "What's in a Name?"). The major work – to commercialize the concept – was still ahead of us.

Besides our presentation of Orbitrap, the ASMS meeting proved important in another way. We presented several additional projects – MALDI-TOFs, GC-TOFs and so on – that generated interest from the "big guys", including Thermo, and we told people that we couldn't develop Orbitrap technology on our own. The consequence was that we started conversations with five major mass spectrometry companies. But the more discussions we had, the more the objections and limitations mounted up like another range of mountains to be scaled (see "Reasons Why Orbitrap Should Not Work", page 30). The main limitation was that it could not be used for continuous ion sources like electrospray, which is the main workhorse of mass spectrometry; but

What's in a Name?

The name Orbitrap actually appeared much earlier than the technology itself. When I first showed the principle of trapping to my colleagues in the autumn of 1996, they asked "so… what is it?" I replied that it was an electrostatic trap, and we decided that it needed a name. I don't remember exactly when I came up with the term Orbitrap, but I think it was during some holiday time when my mind was mulling over the problem. I knew that the name needed to include "trap" but I didn't know what to add to it. I recall writing down several word combinations but they didn't go well together. Then I thought well, ions are orbiting, so it's an orbital trap: orbitrap. I went back to colleagues with the name and they agreed that it was short and clean. Later, when I titled my first paper, "Orbitrap: a new high-performance technique for mass analysis," a reviewer insisted that the name was wrong because the ions are not separated by their orbit but by frequencies of axial oscillation. The axial component should be reflected, the referee said. I was upset that I had to replace the title with some dull technical term, but included Orbitrap somewhere less prominent in the text. Eventually everyone started using it, and it then became a trademark. At some point after the launch there were a few derogatory comments about the name, but Orbitrap caught on like wildfire and any criticism disappeared.

1998
Experimental Orbitrap set-up with pulsed laser source produces first spectra. The set-up continues to produce increasingly high resolving power, reaching 150,000 by mid-1999.

1999
Orbitrap proof-of-principle reported at the American Society for Mass Spectrometry's (ASMS) annual conference in Dallas, Texas, USA. HD Technologies begins discussions with five major mass spectrometry companies and learns of Orbitrap's current limitations.

2000
Thermo acquires HD Technologies in January. Alexander concentrates his efforts on a continuous ion source interface, the primary limitation of the technology.
Analytical Chemistry publishes Alexander's paper, "Electrostatic Axially Harmonic Orbital Trapping: A High-Performance Technique of Mass Analysis (Anal. Chem. 2000, 72, 1156-1162).

Reasons Why Orbitrap Should Not Work

- It is not possible to provide ion packets with the required spatial and temporal parameters for continuous ion sources
- The tolerance requirements on the electrodes are not realistic
- Injection and central slots will ruin resolving power and mass accuracy
- The vacuum requirements are ridiculous and cannot be met
- Ions can not be injected with high efficiency
- A wide mass range cannot be injected and captured
- The image current preamplifier will be destroyed by pick-up during injection
- Noise from the high voltage power supply will overwhelm the preamplifier
- Surface potentials will disturb and scatter ions
- Mass accuracy will be poor because of voltage drift and noise
- Large ion numbers cannot be properly injected or analyzed
- The electrode shape, rotational and radial frequencies will cause unmanageable mass-dependent harmonics

the really scary thing was that all of the objections were justified, including quite a number that we hadn't thought of ourselves.

As daunting as it was, however, knowing the challenges was a good thing. It meant that we could begin on the long road to a commercial product. Each challenge became a development project in its own right.

Lady luck

Thermo was the company most interested in collaborating, firstly, because of our TOF technology and secondly, because they already knew from previous interactions that we were innovative, serious about development, and that we had fun at work. Thermo acquired HD Technologies in January 2000 – just before the Dot-com bubble burst. Pretty lucky.

While Orbitrap technology wasn't actually the major reason for Thermo's acquisition, we still received a due diligence visit from Thermo's top four research scientists (George Stafford, Jae Schwartz, John Syka and Mike Senko) prior to the purchase in November 1999 – the story that opens this article. They were all extremely interested in seeing the technology in action and (following the secret dead pump, electrical short and analyzer-shaking episode) were thoroughly impressed by what they saw. Very lucky.

In fact, we'd had more luck on our side without knowing it. All of our original experiments had been conducted with the original set of electrodes. In parallel to instrument development, we had been trying to make a second set of electrodes and were failing miserably. The working electrodes had been made on a brand-new lathe by a small

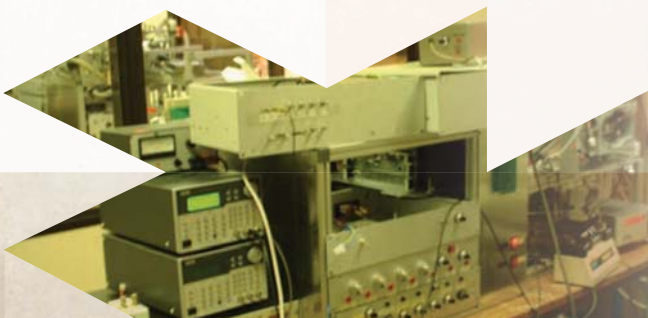
2000–2002
Work on the Orbitrap is expanded. Mark Hardman, Alexander Kholomeev and Eduard Denisov join the team to focus on ion-optical, mechanical and physical design.

2002
Thermo closes the Manchester factory in July and transfers research Bremen, Germany.

2003
A working instrument produced by Masslab is installed in Graham Cooks' lab at Purdue University, Indiana, USA.

2002–2005
The Orbitrap project continues through hell and high water, surviving only through innovative thinking, determination, and a talented and ever-growing team.

2005
The LTQ Orbitrap tandem mass spectrometer is commercially released at ASMS San Antonio, Texas, USA, and becomes the first fundamentally new mass analyzer in more than 20 years.



company nearby; we were never able to produce working electrodes with any lathe, whatever its precision, despite spending years and years trying. Now, of course, almost every electrode that is machined works within specification, but back then that was simply impossible. Had it not been for that original freak success, we wouldn't have the Orbitrap today…

At other times, perseverance and ingenuity kept us afloat. On the problem of interfacing Orbitrap with continuous ion sources, we'd spent ten times more effort than anticipated, encountering numerous problems. Each time, just when it seemed like the whole project would be shuttered, we would come up with some alternative idea. This was because, throughout, development was progressed along parallel tracks: a "main track" where we were going at full speed using maximum resources, and a "back-up track", which was usually higher risk. Several times over the course of the project, the seemingly guaranteed, straightforward solution failed and we had to resort to the fallback – it's a testament to our planning and to the team, which was growing with new talent that included Mark Hardman, Alexander Kholomeev and Eduard Denisov. The eventual solution to the continuous accumulation problem was the C-trap, a novel storage device.

To Germany!

The factory in Manchester was shut down in July of 2002 and the project moved to Bremen, Germany. My family stayed in Manchester so I had to commute for several years. Two people from my group moved to Bremen to work on the project full-time and we got excellent support from the local management, particularly Reinhold Pesch, R&D director at the time. Both he and Bremen site director Juergen Srega gave us whatever we needed, whenever we needed it. They understood that the only way to move forward was to work with the highest intensity possible, which is why they gave us their best scientists and best project manager – Stevan Horning.

The other side of that arrangement is that we needed to show that we could deliver what we promised. Wilko Balschun and Oliver Lange made up the core group of five, which would stay together to deliver Orbitrap. We benefitted hugely from the decades of acquired experience at Bremen but, whatever the size of the organization, it's the core team that matters. You need enthusiasts that are willing to fight and die for the project and the high risk of failure helped fuel that mentality. Personally, I felt another source of urgency: since I couldn't continue commuting indefinitely, I needed to produce results! It just wasn't civilized living between two countries in cities that lacked a direct flight between them. However, although it was personally frustrating, it was successful from a work perspective. When in Bremen, I spent my time in the lab; back home in Manchester I had space for modelling, designing and thinking through experiments.

We gradually plucked a route of success through a more abundant series of failures.

The highest workload came in the run-up to the commercial release of the LTQ Orbitrap tandem mass spectrometer at the June 2005 ASMS conference. Nowadays, a small team like

2008
Single-stage mass spectrometer "Exactive" is launched. Options for electron-transfer dissociation (ETD) and matrix-assisted laser desorption/ionization (MALDI) are introduced.

2011
"Q Exactive" is launched and expands reach to the bench top for routine analysis in proteomics, metabolomics, environmental, food and safety analysis. Next generation Orbitrap Elite also launched.

2013
Orbitrap Fusion Tribrid is launched, combining three mass analyzers – quadrupole, Orbitrap and a linear ion trap.

How Orbitrap works

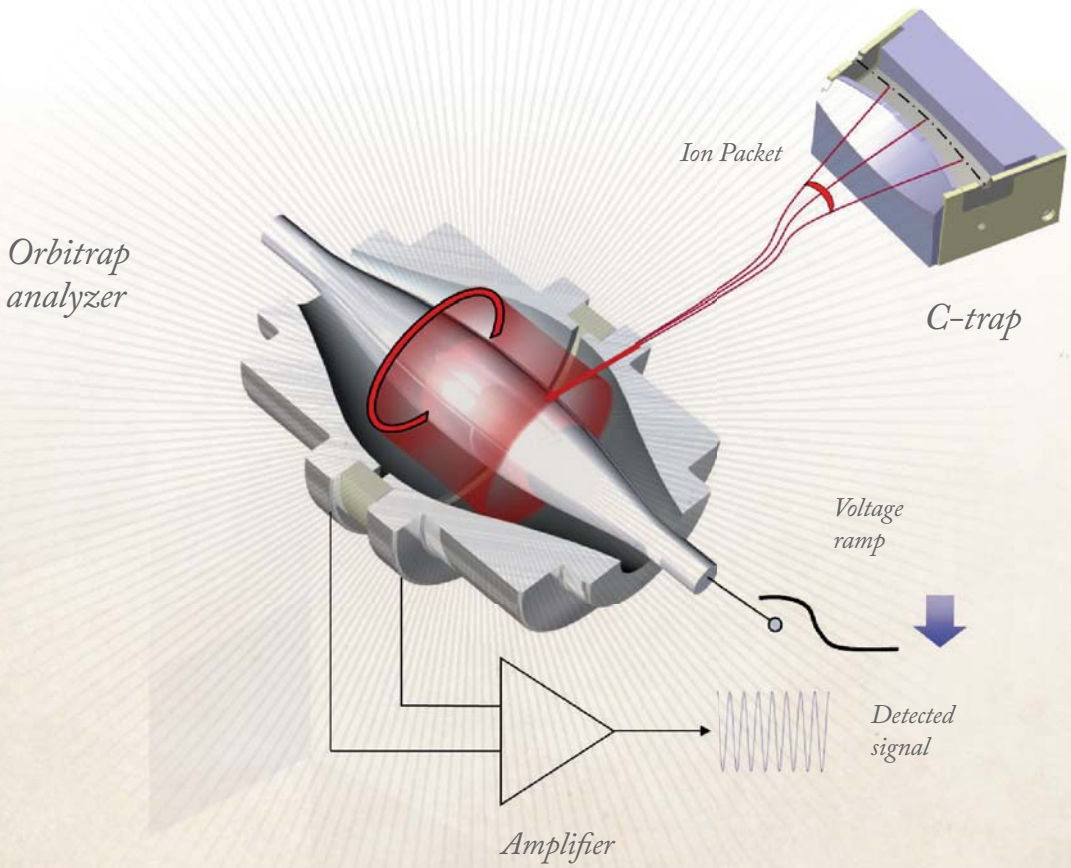
The Orbitrap consists of an outer barrel-like electrode and an axially symmetrical central spindle-like inner electrode. To inject ions, the field between the electrodes is first reduced. The ions enter the field and are squeezed closer to the centre of the trap by an increasing electric field, like stars to a black hole. After the mass range of interest has entered the Orbitrap, the voltage is stabilized and detection may take place.

The ions move along complicated spiral cycles that have three components:

- rotational movement
- radial movement
- axial oscillations along the central electrode

Only the harmonic axial frequency (ω) is independent of the energy and position of ions but dependent on their mass-to-charge ratio (m/q). It is represented by: $\omega=\sqrt{(k/(m/q))}$, where k is the force constant of the potential.

Axial oscillations are detected by the image current at the two symmetrical pick-up sensors of the split outer electrode.



ours would never attempt such a launch. The progression from breadboard to prototype to pilot, and so on, was taxing on everyone – and resulted in a few years of supporting unusual situations with customers. However, the sheer improvement in performance that Orbitrap delivered more than justified these original teething troubles; it was, after all, the first fundamentally new mass analyzer for more than 20 years.

Job done?

Fifteen or 20 years ago, a small group of colleagues set out with the spirited intention of moving the needle – doing something that would really change the face of our industry. What I discovered is that it's one thing to have a scientific curiosity that everybody loves, it's quite another to deliver something to labs, where it matters.

We did it. And, unusually, the entire development, from proof of principal to mass production, took place within one group. After the Orbitrap instrument was launched, it was extremely rewarding to witness the improvment in results that researchers achieved and to see some of their technical problems solved. At launch, the LTQ Orbitrap was the most expensive system on the market and, like most new technology, it penetrated the early adopters first and only much later did it enter more routine labs.

It's always difficult to see the full impact from the inside; when you are fighting for something from morning until night you don't always hear what's happening in the field. Only later did I understand the scale of change. Competitors were generally astounded by Orbitrap technology. They respected the science fully and always expressed their highest regards for the entire technology. And their reaction to the introduction of Orbitrap helped to accelerate the entire field as it woke them up and got them moving forward. I believe that mass spectrometry users have much better technology now than they would have had without our product – whether they are Orbitrap users or not.

The Future with Orbitrap

I am sometimes asked if I am surprised that Orbitrap technology is still relevant today. My answer is no, I am not; actually, I believe that the Orbitrap age is only just beginning.

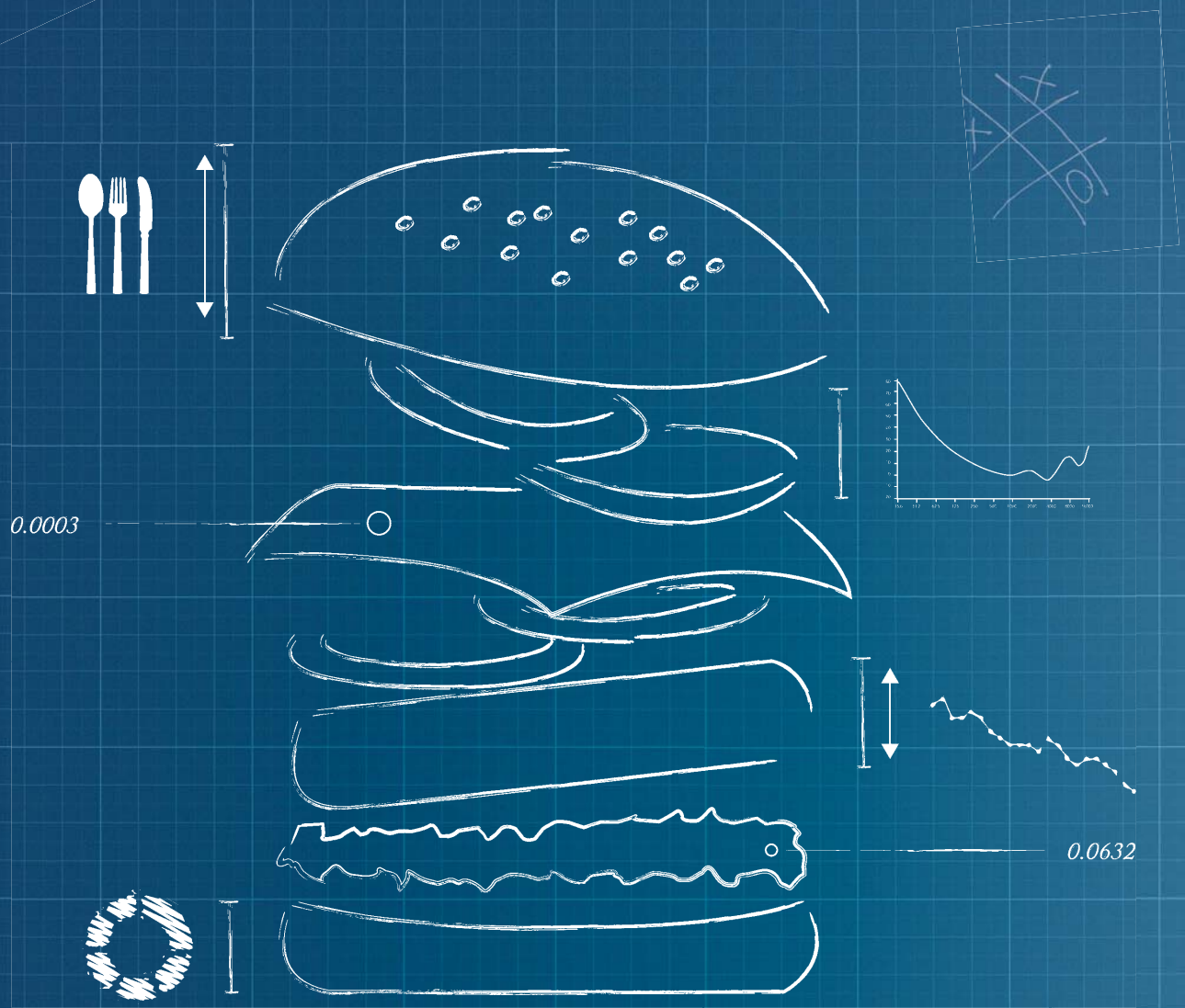
The new Fusion Tribrid obviously represents the pinnacle of Orbitrap development to date. It's the tip of the pyramid and the base is rapidly expanding with routine instruments, like the Exactive and Q Exactive. The pyramid will continue to grow by enabling new applications, to the point where high resolution and accurate mass become as routine as nominal mass analysis by triple quadrupoles. I believe that environmental, food, forensics, toxicology, doping – in fact, all analyses – should be high resolution and accurate mass in the end. To achieve this, two main challenges must be overcome. First, we need to constantly crank up performance to match the increasing complexities of samples and increasing expectations of users (and keep up with any competition). Second, we have to make the technology both bulletproof and routine in operation. Today, quadrupole technology is routine, but in the 1950s and 60s it was the top end, highest of high tech, with only a few people able to make it work. That's the transition that Orbitrap technology is going through now. We need to switch from the current, relatively fragile and difficult-to-tune machine, to an instrument that "just works". These two goals – performance and usability – are demanding, but achieving them will reap rich rewards from a massively increased user base.

So far, Orbitrap is used mainly with electrospray and atmospheric ion sources, but in the future it will be used with all other ion sources. My main interests and expectations are in the clinical analysis of peptides and proteins – the entire promise of proteomics is actually strongly linked to Orbitrap technology. While the field is not yet delivering on the optimistic promises of ten years ago, both proteomics and clinical analysis are currently much further ahead than if we had continued the linear development of the early days.

I feel lucky to have gone through all phases of the development of Orbitrap. Today, I am as excited about the technology as I was in the beginning, but perhaps in a different way. Plus, we have the challenge to produce something that's as good as, or even better than, Orbitrap; that will be difficult! For now, I am focused in part on front-end development with ion sources and research into new types of analyzers. I am also passionate about improving the use of analytes. At the moment we throw most of them away but we should be able to get to the point where we use analytes completely. These are tough challenges but the success of Orbitrap has given me some of the resources and belief that I need. If only I had more time! University collaborations, conferences and management all compete for attention, which leaves only a small percentage to concentrate on these hopes for the future.

My big dream is that one day every hospital will have an Orbitrap mass spectrometer – that would really have the greatest impact on society. There's a long way to go and, as proven by this story, whether it happens or not depends on many different circumstances, but also on me.

Alexander Makarov is Director of Research, Life Science Mass Spectrometry, Thermo Fisher Scientific, Bremen, Germany.



Chewing Over Food Analysis

Recently, we got round the table to sample the views of five experts on the future of food analysis. Is separation science still the greatest thing since sliced bread, or are there bigger fish to fry? Whether you find their views to be the cream of the crop or nutty as a fruitcake, they'll certainly provide you with food for thought.

What are the hot potatoes in food quality and safety?

Michele Suman: In general, we need to pay more attention to food fraud and the associated risks – issues that are strongly related to globalization of the market and economic crises. I also see a number of more specific issues. There should be an increased focus on allergens and genetically-modified organism (GMO) issues. Regarding chemical contaminants, emerging and masked mycotoxins present a complex challenge in terms of analysis and risk assessment. We must also continue to be vigilant on the impact of veterinary drugs and pesticides; their widespread use has consequences for raw materials and finished products. Additionally, advanced industrial technologies are introducing new issues, such as those related to nanoparticles. Finally, there is the ongoing issue of food packaging materials: the absence of toxicological evaluations and harmonized/comprehensive legislation platforms suggests that risks connected with the specific migration of substances from packaging into foodstuffs will remain a major topic for the next decade.

Rudolf Krska: I would highlight incidents related to chemical contaminants, including natural toxins, in feed and food. There have been a number of these across the world and only recently have they attracted media attention. To give an example, earlier this year 45,000 metric tonnes of corn contaminated with Aflatoxin B1, originating in Serbia ,was delivered to 3000 farms in northwest Germany for animal feed. Fearing that milk from the cows could contain the cancer-causing metabolite Aflatoxin M1, the German authorities banned milk collection from hundreds of dairy farms.

Food and feed safety is of increasing concern to consumers, governments and producers alike. This is the result of a truly global marketplace with almost limitless production and distribution options, but it is also impacted by increased public awareness of health and food quality in general.

The list of potential trace chemical contaminants in foods is a long one. They might originate in natural sources (e.g., mycotoxins, phycotoxins), environmental contamination (e.g., PCBs, dioxin-like compounds, pesticide residues, perchlorate), migration of chemicals from packaging materials (e.g., phthalates and bisphenol-A), veterinary drug residues, by-products from food processing (e.g., acrylamide), or from other forms of intentional and unintentional adulteration (e.g., melamine in milk products, ethyl carbamate in wine). Furthermore, instances of emerging contaminants, such as perfluorinated organic compounds entering the food supply, are also on the rise. This list is far from complete and must be extended and updated regularly.

The occurrence and risk management of (hidden) allergens in food is another important food safety topic; labeling information on foods must be accurate to allow consumers to make informed choices about their diet.

Michel Nielen: The major issues? Contamination by natural toxins... and fraud.

Do you believe that all the main issues – from soup to nuts – are being adequately addressed by (inter)national research programs and/or industry?

YP: Not at all! Financial support is not sufficient to guarantee proper development in these fields and the industrial investment in R&D is low.

MS: Even though there is a great range of potential issues, I am optimistic for the future. Much progress has been made over the last ten years through devoted national and international projects. Furthermore, the attention of stakeholders, from raw materials producers to end users to retailers and authorities, is clearly stronger than in the past.

RK: I agree with the European Food Safety Authority (EFSA) that European consumers are among the best protected and best informed in the world when it comes to risks in the food chain. The EFSA establishes independent scientific opinions on known and emerging contaminants and is the keystone of European Union risk assessment regarding food and feed safety. (Disclosure: I am a member of the EFSA working group on Fusarium toxins.)

On the research side, the European Commission has funded projects to tackle the increasing need for faster and more cost-efficient methods for the determination of a wide range of chemical contaminants in different food commodities; examples are CONffIDENCE (www.conffidence.eu), BIOCOP (www.biocop.org), MYCORED (www.mycored.eu) and QSAFFE (www.qsaffe.eu). These initiatives should reduce the levels of contaminants, such as mycotoxins, along the whole food and feed chain. And, since they reduce the cost per test, they will permit more samples to be monitored, further contributing to safety. My hope is that further funding for food safety and innovative food contaminant screening will be available within EC's Horizon 2020 program.

MN: With respect to fraud, I have doubts. Governments do not necessarily associate fraud with quality and safety. However,

The Panel

Rudolf Krska
Professor for (bio)analytics and organic trace analysis and Head of the Department for Agrobiotechnology (IFA) at the University of Natural Resources and Life Sciences (BOKU), Vienna, Austria. He obtained his degree in chemistry at the Vienna University of Technology and is an expert in food and feed analysis by chromatographic, mass spectrometric and immunoanalytical techniques.

Michele Suman
"When my mother mentioned the possibility of me becoming a chemist at primary school age, my response was, 'No way!'" Despite his initial skepticism, Michele Suman became a chemist and then took a masters and doctorate in chemistry and materials science before eventually landing the role of Food Chemistry & Safety Research Manager at Barilla SpA. There since 2003, he has been working in an international contest on research projects within the field of food chemistry, food contact materials, sensing and MS applications for food products.

Hans-Gerd Janssen
"A chemical engineer is what I wanted to be," says Hans-Gerd, and so, decided not to go to a "regular, dull" university but to a University of Technology. "I then got annoyed by the approximate nature of chemical engineering." Of special interest to Hans Gerd now are food samples. "I want to understand why certain foods are safe and of high quality whereas others are poor. Analytical chemistry, my field of work for almost 30 years now, is key to that," he says.

Yolanda Pico
Yolanda is professor for Nutrition and Food Science and Head of the Research Group in Food and Environmental Safety (SAMA-UV) at the University of Valencia, Spain. She works in the development of new analytical methods to determine organic contaminants in food and the environment, identification of unknown compounds by LC-MS, microextraction, and other separation science.

Michel Nielen
Michel is Professor and Special chair on Analytical Chemistry at RIKILT Wageningen University & Research Centre in The Netherlands. His research focuses on bioactivity-related detection and identification technologies for chemical contaminants in the food chain, ultimately leading to the identification of emerging unknown bioactive contaminants.

having experienced the melamine scandal, we know that there is a very serious public health component to fraud. The key factor is that one should be ready to face the unexpected: nobody was analyzing for melamine in foods prior to the incident…

With respect to natural toxins there are already substantial efforts from industry and from collaborative research programs. The crucial thing here is that only a limited number of natural toxins are being tracked due to a lack of standards and lack of knowledge about all the chemical structures produced in nature.

What analytical challenges are likely to upset the applecart?

RK: Analytical needs have to be considered in the light of existing regulations. For example, the Feed and Food Control Regulation (EC) No. 882/2004 requires that official tests be carried out for identified risks. As a result, the demand for simplified and rapid test methods at critical control points over the entire chain has never been greater. Novel screening tools should have multi-analyte, multi-class capability; that is, they should detect, in parallel, multiple contaminant parameters within a short period of time. There is also a great need to develop and improve systems of traceability and authenticity for the major food and feed materials used. Despite ongoing activities, we still need an intense effort to combine existing testing methods and emerging technologies, including fingerprinting technologies and metabolomics, into a comprehensive analytical strategy to determine the best application for food safety monitoring at ports, feed mills and laboratories.

Potential contaminants and allergens cover a wide range of chemical and physical properties, ranging from lipophilic to hydrophilic, from volatile to non-volatile and from small molecules to large proteins. Many of these analytes have poorly understood toxicological or allergenic effects and the maximum allowable levels set by regulatory agencies are often driven by the achievable limits of detection. Matrix-independent methods and low quantification limits are required for surveillance of recognized and newly-identified contaminants to aid risk assessment. The use of solid-phase extraction (SPE) techniques in combination with mass spectrometry (MS) detection will be crucial for success. Besides sensitivity and specificity, this offers the capability to process a large number of samples quickly. A final point: there is a need for appropriate reference materials – particularly evident in the area of allergens – to assure comparability.

MN: First, there is a need to develop analytical methods for unexpected and unknown contaminants originating from

natural toxins and fraud issues. Secondly, miniaturization is key – bringing the analytical lab to the inspectors, to the food truck drivers, and to the consumers.

Which analytical techniques could sell like hot cakes to solve the major challenges?

MS: One analytical challenge for food quality is the development of specific strategies devoted to monitoring the shelf life of products. To this end, high-resolution (HR)MS combined with appropriate chemometric tools will be increasingly exploited for applications in both food quality and safety. High-throughput, reliable and rapid screening technologies represent another necessity/opportunity in the food-industry sector.

MN: High-end MS and nuclear magnetic resonance (NMR) are crucial for structure elucidation of unknowns. Ligand-binding assays are crucial for miniaturization.

YP: Biochemical arrays and liquid chromatography (LC)-MS.

RK: MS-based analytical methods (gas chromatography (GC)-MS, quadropole time-of-flight (Q-TOF), ultra-performance LC-MS/MS have been key for the quantification of chemical contaminants and residues in foods and for the investigation of the metabolism of these toxic compounds. Metabolite profiling represents an extremely useful tool that has applications in many aspects of food safety. One example is a multi-analyte method that we recently developed, which is capable of quantifying 320 toxic fungal, bacterial and plant metabolites in cereals and food products. A multi-toxin method has also been successfully applied to the analysis of human urine to assess the exposure of individuals from European and African countries to various mycotoxins.

For easy-to-use, rapid testing, new methodologies are being developed. Despite innovative multi-analyte strip-test designs, at present the most common rapid assay formats are still immunoassays.

Which areas in food analysis are like finely aged cheese and therefore less in need of attention?

MS: I think that nutritional labeling analysis (sugars, micro/macronutrient, fibers, etc.) and rheological testing represent two mature areas that pehaps do not have an urgent need to be renewed.

YP: Classical food characterization and traditional food control methods based on trituration.

Hans-Gerd Janssen: There is not a single analytical measurement in food analysis that is mature. Unlike clinical analysis, where fully automated systems analyse numerous clinical parameters from small blood samples, for a few euros per sample and with no risk of making mistakes, in food analysis, matrix effects can never be neglected. Variability between samples can be large, interferences can occur, and so on. Even the simplest measurements, such as total fat, moisture or pH, can be wrong or easily tampered with. Clearly immature!

MN: Pesticide and dioxin analysis are pretty well established…

What are the hard analytical nuts to crack?

MS: On the chemical side, the development of multianalyte methods that permit easy and precise quantitation of different classes of molecules is important. A special case is represented by masked mycotoxins – new analytical methods should be able to simultaneously differentiate and assess various types of bound forms within food matrices. Staying on the microbiological side, I see a need to develop analytical methods for rapid pathogen detection and allergen evaluation, and their evolution along food-processing steps. And of course, there is always the aspiration for analysis "in the field", which means a strong focus is needed on instrument portability and miniaturization.

HGJ: The real need, put simply, is this: reliable methods that provide accurate results even in the hands of less experienced operators, in as short a time as possible, and at low cost per analysis. And this applies to trace levels of contaminants or flavor/fragrances as well as main ingredients. Another requirement: methods that are up and running in minutes rather than days or even weeks.

YP: Fingerprint characterization, and the determination and characterization of proteins and lipids.

MN: Localized (spatially resolved) analysis for contaminants.

Can mass spectrometry continue without chromatography or vice versa? Can we have our cake and eat it?

RK: Target analytes in foods are often chemically highly diverse, which precludes a single common clean-up procedure. Simple so-called "dilute and shoot" approaches have become popular in

multi-analyte determination. Here, the crude extract is simply diluted (to reduce matrix effects) and injected into the LC-MS/MS system. However, achieving sufficient selectivity to separate these analytes from interfering matrix peaks is a major issue, especially with dilute and shoot methods. Separation science has been key to satisfactory validation data for the tested contaminants and will continue to play an important role in food analysis despite the highly sophisticated mass spectrometric tools that have become available in the last decade.

HGJ: That is the question! Except for desorption electrospray ionization (DESI) and direct analysis in real time (DART), which are qualitative screening tools, all mass spectrometers are (and will continue to be) connected to a chromatograph.

MN: I believe the price of MS detectors in separation science will drop to the costs of a diode-array UV detectors or even lower – chromatography will not continue alone.

So, what will be the flavor of separation science in future?

HGJ: The quality and safety of food products are predominantly affected by trace compounds rather than the main ingredients. Accurate information on these trace components requires their isolation from the bulk and separation from each other. Of course, separation methods are indispensible for that. For compounds present at intermediate levels, NMR or direct inlet MS techniques can be used. But truly accurate analysis of compounds at low levels, in complex samples, requires separation science.

However, separation methods take too long to implement. A question is asked today and an answer is needed by tomorrow. For separation scientists, it will become impossible to deal with such requests – we need days or weeks to implement methods. If other techniques provide faster answers, they will likely be accepted even if the results are less reliable. There is no future for good food analysis without separation sciences, but we should be mindful that other mediocre methods do not become the standard.

YP: The future of separation science within food analysis is very promising because of the highly complex matrices involved and the need to separate target (in a wide sense) molecules from interfering compounds. By focusing on better, faster separation, by eliminating interfering compounds, and by providing selective extraction methods tailored to particular molecules, that future is guaranteed.

MS: Separation science is firmly connected to mass spectrometry science. Taking this into account, further improvements in the UHPLC direction can be expected, for example, in terms of new stationary phases to reduce matrix effects or to separate isomers/close chemical classes. The foods of the future will be increasingly complex in terms of combination of tastes, ingredients, functional molecules, and so on. Analytical goals will only be achieved if separation science continues to exist.

MN: The complexity of some food and feed sample matrices means that we will be unable to provide quantitative data without separation methods.

And which analytical techniques will be top banana?

RK: Emerging methods, such as biosensors, nanomaterials, and electronic noses and tongues, show great promise. Other innovative methods in the area of food safety include near infrared hyperspectral imaging, quantum dot-loaded liposomes for ultrasensitive on-site determination, and easy-to-use multiplex dipstick assays.

Metabolomics – based on HRMS and GC-MS – also has great potential given its ability to determine hundreds to thousands of secondary metabolites and other compounds present in food. For me, this aspect is the most fascinating but also the most complex area of analytical chemistry and food analysis.

MS: In my opinion, HRMS is the most promising technique. But there is also interesting and relevant progress being made in rapid, non-destructive techniques, such as FT-NIR, biosensors, and immuno-devices. From a morphological information point of view, a brilliant future can be seen for field-emission environmental scanning electron microscopy. Finally, the development of more robust and flexible artificial e-nose and e-tongue platforms could boost synergy between sensory and analytical sciences.

YP: LC, SPME, capillary electrophoresis, lab-on-a-chip. Basically, all separation techniques will continue to play an important role.

HGJ: Localized compositional analysis methods, for example, MALDI imaging. Not only can such methods give us information on bulk compositions after homogenization, but they also tell us which molecule is present where, what its neighbors are and what interactions are involved.

MN: Ion mobility MS may take over from some conventional separation methods.

Do separation scientists need to change their attitude/ focus/scope, if they want to cut the mustard?

MS: Separation scientists should focus on how to reduce or avoid undesired matrix effects, depending upon food composition. And they should work actively towards miniaturization.

HGJ: Analytical scientists should work with food scientists. It is all about working together. We should listen to the needs of our users and do what they need, not what we find interesting. Analytical chemistry should co-operate with people in the application domains. This does not mean we should just measure what others tell us to measure, we should consider together which measurements can really contribute to food quality and safety.

YP: Personally, I don't think so – recent advances in techniques and their application to food analysis demonstrates the good health of the field.

Did we omit an essential ingredient?

MS: Who are the new generation of food chemists that we need to train? What should be their main competencies be? And what level of intra/inter-exchanges between academy and industry along their educational path is necessary?

HGJ: How can we predict food quality, safety and consumer preference from food analytical data? Or even: can we predict food quality, safety and consumer preference from food analytical data? I understand certain aspects of this question, but would love to hear the comments of others.

Profession

Leadership
Talent Development
Career Planning

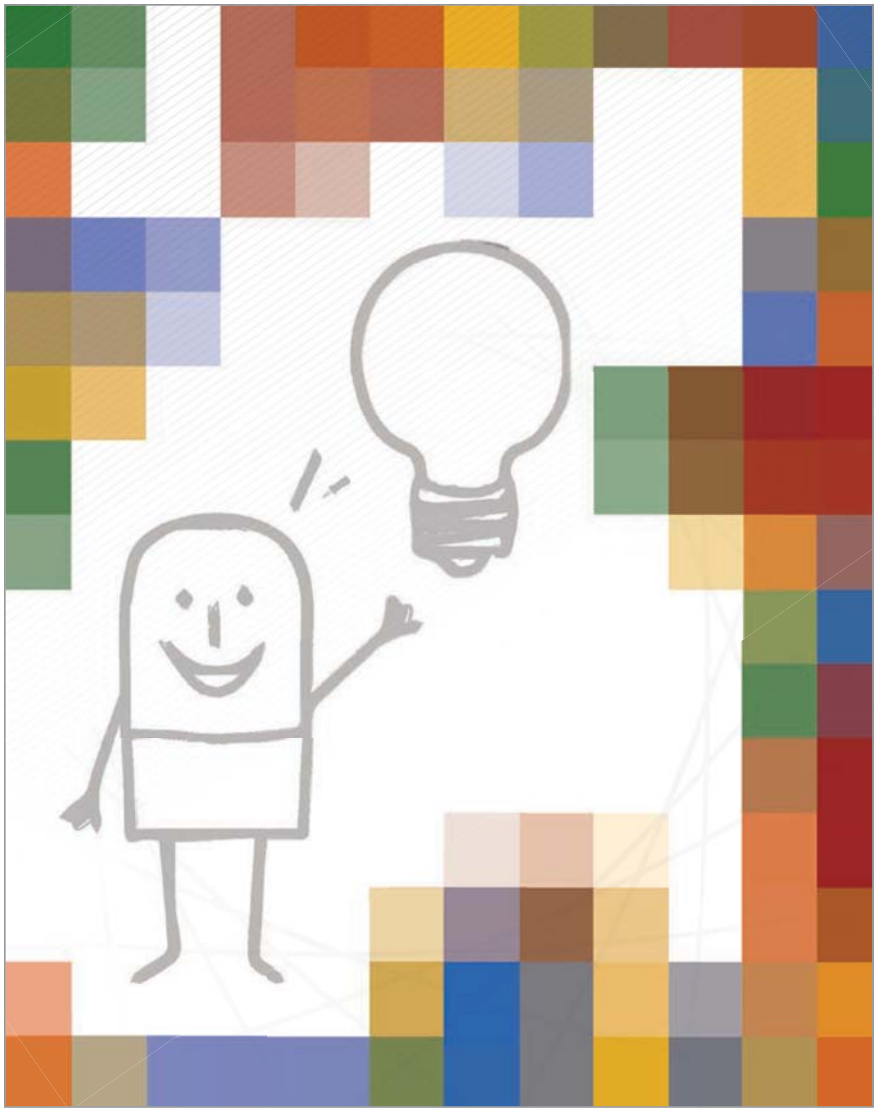
Innovation is Child's Play

How analytical scientists can innovate by setting aside the normally essential critical and logical thought processes that define science, and embracing the lost skill of imagination.

By Jon Platt

Innovation and analytical science can be uncomfortable bedfellows. Successful innovation depends on behaviors far more than process, in particular the kind of expansive, creative behaviors that are rarely ingrained in the culture of science-based organizations. If you have ever been in a meeting and suggested a leftfield idea, only to have several colleagues tell you immediately why it won't work; you have experienced a clash of behaviors.

Trying to find an unusual solution to a problem is an expansive behavior, while subjecting an idea to criticism and skepticism is reductive. Successful innovation demands the use of both. Over-zealous use of reductive thinking can be particularly acute in the field of analytical science, where analysis, skepticism and data-driven objective evidence are highly valued. Of course, subjecting new ideas to reductive analysis and questioning is important to innovation, but you need to have those new ideas in the first place, and to give them room to grow and develop before they are judged.



Child's play

Ideas are key in moving analytical science forward; original ways of thinking are crucial in finding

solutions to ensure safe food and water, reliable medicines, and sustainable energy. So how can we evolve our ways of thinking to effectively meet these needs in a world where problems seem to win the race against progress?

The first part of the answer lies in recognizing the need for distinct phases of expansive and reductive thinking in any innovation initiative. The trick is to get everyone working on the problem to move in step, using expansive or reductive thinking as needed, but at the same time. Signaling can help make this shift explicit for your team. The signal, in its simplest form, could be how a request is phrased; asking your colleagues to help build an idea with you (expansive) or seeking help in judging one (reductive). Bear in mind that in a world where reductive thinking dominates, simply asking colleagues "what do you think?" invites judgment by default.

The good news is that we are all born with an incredible ability to think expansively. If you have ever given a small child a gift, only to see more fun being had with the box it came in than the present, you have witnessed an expansive thinker at work. Imagining alternative possibilities is at the very heart of expansive thinking – just like a child seeing a car, a house, or a spaceship in a cardboard box. The bad news is that while we are born with this ability, it is gradually trained out of us; first of all, by an education system that teaches us there is only one right answer to a problem, and secondly in our working lives, where this process often continues.

In 1968, George Land gave 1,600 five-year-olds a creativity test used by NASA to select innovative engineers and scientists. He then re-tested the same children at ages 10 and 15. The test showed that 98% of five-year-olds registered genius-level creativity, but this declined sharply to 30% at 10 years and 12% at 15. The same test given to 280,000 adults placed only two percent with genius-level creativity. Yet while our ability to think expansively and creatively may have atrophied over time, it can be recovered. We all have it within us to re-learn how to be a 'genius child' once again – and to take this fresh thinking into the field.

When and where?

I have spoken on the subject of creativity to organizations all over the world and collectively asked thousands of people when and where they have their best ideas. The most common answers include "out walking", "in the shower", "in bed early in the morning". Nobody has ever answered "in a busy meeting at work", which is because, in meetings, we are usually in a Beta mindset. Often called 'busy Beta', this mindset is characterized by a high state of alertness and equips us for logical thinking and decision-making. When walking or showering, we can access our Alpha mindset, in which relaxed visionary thinking becomes possible. Deep meditation can take us further still, to Theta, which is an almost dream-like state.

Expansive thinking is helped by being in Alpha or Theta state so no small wonder that it is impaired by a busy and pressured environment. Create conditions where you and your co-thinkers can relax and become playful. People need to feel that they are working in a safe bubble where a new idea will be positively supported and explored.

Though ideal settings for creating and handling large volumes of data, laboratories are far better for dissecting established theorems than for creating new solutions. Find an inspiring space to work away from the grey windowless boardrooms or labs where most brainstorms are attempted. Surrounding people with color, sensory stimulus and other aids helps to achieve that Alpha state, which can be the ideal catalyst for a truly innovative reaction.

Above all, avoid the temptation to think that a serious problem demands seriousness of both mind and environment. Anxious, frowning people rarely have brilliant new ideas.

Growing seeds

A new idea is like a seed. Like a seed it's hard to see whether it will develop into a weed or a flower or a tree without time to grow. Along with creating the right expansive environment comes another behavior we call "greenhousing". Just as a greenhouse protects young plants, greenhousing is a way of protecting new ideas as they grow.

Principally this is done through attitude and language. First of all everyone working on the problem must adopt the attitude that every new idea has potential and that their role is to look for ways to add depth and positively build on it.

Reject language such as "Yes, but...", "That will never work", "The regulations won't allow that". Instead, insist on language like "Yes, and…", "That could be even better if…".

Many of the greatest discoveries were unplanned. Creating a fresh paradigm for analytical science necessitates the nurturing of a culture of innovative thinking. In the first instance, look at an idea's potential significance, rather than its limitations. Once an idea has been developed for long enough to explore its potential, then the team can consciously switch into reductive mode and evaluate it.

Seven Seeds of Innovation

Set aside critical thinking and cynicism ahead of brainstorming sessions.

Unleash the genius streak of creativity you were born with but lost through years of pragmatism.

Understand that imaginative thinking is best supported by a relaxing environment. People have their best ideas whilst in the shower or on walks rather than in tense boardroom meetings.

Avoid the temptation to think that a serious problem demands seriousness of mind and environment. Anxious, frowning people rarely have brilliant new ideas.

Give new ideas room to grow. "Greenhousing" protects an idea up to the point that it is sufficiently developed for useful critical evaluation.

Choose the right mindset over skills, when it comes to selecting members of your team.

Recognize that the solution may already exist outside the world of your problem.

Mindset over skillset

If you have a choice with whom you collaborate, go one step further and actively recruit on the basis of mindset and attitude rather than simply skills.

A few years ago, I had a conversation with Scott Forstall of Apple, who led the team that developed the iPhone, arguably one of the most influential innovations of the past ten years. I asked him the secret of creating such a series of technical breakthroughs and his reply was that success was totally dependent on recruiting a team with the right mindset.

Forstall is a follower of psychologist Carol Dweck, whose work on the links between success and attitude are influencing a generation of innovators. In particular, Dweck describes how a growth mindset differs from a fixed mindset. Put simply, a growth mindset is characterized by a love of learning, a reduced fear of failure and a willingness to try out new things. A fixed mindset on the other hand describes a pre-disposition to exercise a skill you already have: to get success by repeating something you know you are good at. Repeating the same experiments with only minor alterations is an essential theme in creating effective science, but sometimes it's necessary to take inspiration from technological innovators and start from scratch.

Scott Forstall knew that the journey to create the iPhone would be characterized by the need to solve multiple new technical problems, many of which could not be anticipated at the outset. So for him, a team with a strong growth mindset, who were willing to learn new skills and grow together, was essential.

The bigger the problem you seek to solve, the more the mindset of the team will determine whether you succeed or fail.

Another world

One of the paradoxes of innovation is that the more experience you gain in a certain area or task, the harder it becomes to think of a new way of doing it. Organizations often fall into the trap of convening experts as a way to find new ideas, without realizing that deep expertise can be a hindrance to innovation.

The answer lies in developing stimuli to see the problem through fresh eyes whilst making effective use of experience. One useful technique, called "related worlds", is based on the premise that whatever your problem, it's likely that something similar will have been solved somewhere else, probably in another field altogether. For example, the underarm roll-on deodorant was developed by asking, "who else has solved the problem of applying liquid uniformly to a surface?" Inspiration was taken from the ballpoint pen.

Above all, the path to successful innovation lies in adopting or re-discovering expansive thinking skills and applying them in a spirit of constant experimentation.

Increasing the level of innovation in analytical science is all about looking beyond the tried-and-tested, and pre-empting the science of tomorrow with inspirational solutions.

Jon Platt is the leader of the healthcare practice at strategic innovation consultancy ?What If! (www.whatifinnovation.com)

Further reading:

Sticky Wisdom, by Dave Allan and Matt Kingdon
The Science of Serendipity, by Matt Kingdon
Mindset, by Carol S Dweck

Don't miss next month's issue, where we showcase the Top Ten Innovations of 2013.

February 18–20, 2014
Crystal City Marriott at Reagan National Airport, Arlington, VA

Symposium Co-Chairs:
Steven Cohen, *SAC Analytical Consultants*
Linda Narhi, *Amgen Inc.*

ABSTRACT SUBMISSION DEADLINE:
November 22, 2013 for oral presentation
January 17, 2014 for poster presentation

HOS2014
BECAUSE STRUCTURE MATTERS

3rd INTERNATIONAL SYMPOSIUM ON HIGHER ORDER STRUCTURE OF PROTEIN THERAPEUTICS

SCAN to browse CASSS for program updates at casss.org

CASSS™
AN INTERNATIONAL SEPARATION SCIENCE SOCIETY
www.casss.org

Business

Economic drivers
Emerging trends
Business strategies

How to Establish a Consultancy

From a seventeen-year vantage point, I offer these recollections into the development of a technology-based consulting business.

By John Coates

The key steps in starting your own consultancy are, (a) possessing the motivation and courage to start, (b) getting the timing correct, and (c) having the guts to see it through. Of these, the third quality is often the most important; almost every start-up goes through a turbulent period where persistence in the face of adversity is required. The other essential piece of information you must have from the outset, is what success really means to you. In setting up Coates Consulting, for me it was recognition, and the ability to bring in new clients and to cultivate referrals.

Preparation

Coates Consulting was established in July 1996. In concept, it was formed in my mind several years earlier.

As early as the start of the 1980s, I realized that the business model in the professional world was changing. In my case it was the instrument business; I'd enjoyed a professional technology career in one of the largest instrument manufacturers, Perkin-Elmer Corporation, which at the time was a $1 billion company and the world leader in the markets that it served. The company was morphing from a multi-technology base (in the 1970s) to a more focused, market driven technology base in the 1980s and beyond. This was a market-wide changeover, with companies moving from the traditional "lifetime" appointment for a company scientist, to a business model where the technical people were an important commodity – as long as the business was profitable, the market expanding and there was potential for continued growth. While there was still some job security for scientists and technologists in the commercial world, it was dwindling, and it favored the politically savvy; the more independent-minded were often removed from the business. This was before the technology "bubble" of the late 1990s, and at a time when companies were inclined to hire consultants rather than hire specialists in full time positions. The time was a ripe for the formation of Coates Consulting.

In the mid-1980s, I joined an emerging instrument-based company, Spectra-Tech Inc., which had been formed a few years earlier by an entrepreneur in the scientific instruments business, Don Sting. Spectra-Tech was a classic small business: limited in budgets but confident in investing in itself, lacking in bureaucracy and run by individuals who made bold decisions. It was the perfect training ground for a "youngish" person who wanted to learn to become an entrepreneur. I learned about business and marketing on the job, both of which are essential to be successful in a crowded market place. As a consultant, you are the business and you need to be able to get yourself known on a very small budget.

Working for a successful small business was a useful first step. The second was to get out in front of as many audiences from as many different industries as possible. I had been doing this since the mid-1970s at analytical and scientific instrument conferences in Europe, the Americas, Asia, and the Soviet Bloc. If you plan to be something of a generalist as a consultant you should address as many different industries and applications as possible during the "information gathering" stage.

In my career between the mid-1960s and mid-1990s my business title changed from applications chemist, to staff scientist, to marketing manager, to business unit manager. Titles mean little

if you truly want to be an entrepreneur, but they provide a means to gather information and expand the scope of your résumé.

My third step in this career-expanding period was to develop a true business network. I don't mean social networking through Linked-in and the like, although they are part of it. It is important to balance the speed, convenience and effectiveness of the modern social/business networks and the benefits of firsthand communications with a known and trusted resource. Your business network is formed over years, even decades, for the most part as face-to-face relationships. Email helps in initiating interactions but it can't match the benefits of a handshake and physical eye contact. The ability to observe and interpret body language is essential. A strong personal business network is critical during the first few months of starting the business, and remains essential for maintaining and growing the business in the first two to five years.

As a technology consultant, a fundamental element of the service you provide is the ability to turn on a dime and provide accurate information to a client or a potential client. You are professionally judged and rated by your ability to respond with real, personal experience-based information, and not regurgitated information obtained from "Googling the Internet". Consultants' reputations, good or bad, are made on the basis of the information they provide. Good ones provide fast and accurate practical information that truly solves a problem; their response is customized to the question asked or the facts required to resolve the issues.

Getting started

Working at a company, it is easy to feel comfortable and be overconfident about job security. The truth is, few positions are secure and decisions to hire or fire can be almost on a whim, even in the biggest corporations, where decisions are made quarter by quarter. That understanding motivated me to plan Coates Consulting.

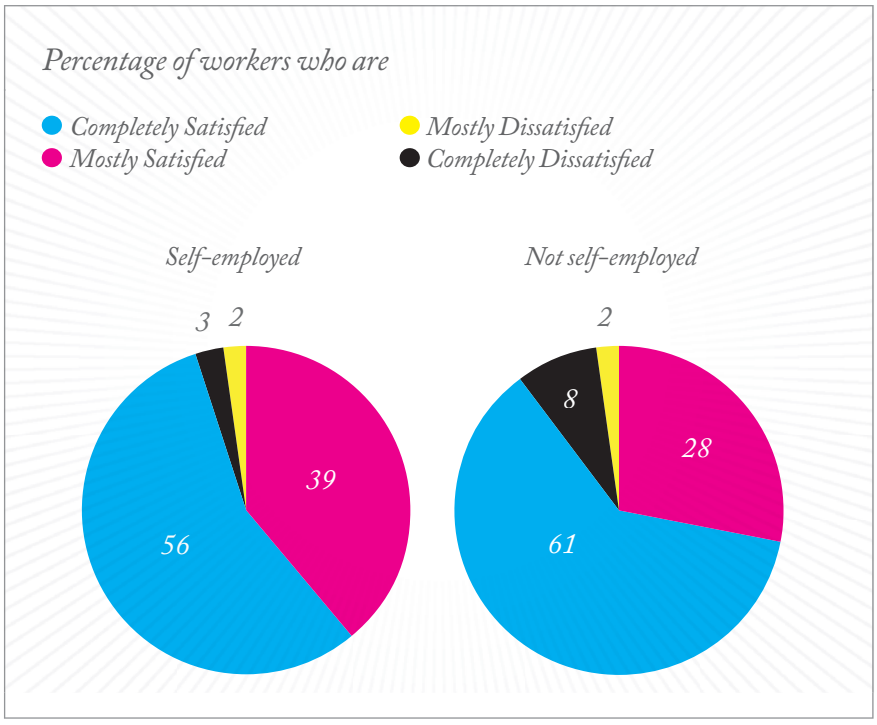


Figure 1. The Self-Employment Paradox. According to a report from the Pew Research Center*, self-employed people, on average, make less money, work more hours, and experience more work-related stress than the wage employed. However, they also have higher job satisfaction ratings than those who work for others.

Timing is another crucial issue (see Figure 1). In my case, I made the decision to set up on my own five years before I started. Letting go of a regular salary and/or having family responsibilities tends to put the decision off. However, if you "see the writing on the wall" then plan on that becoming reality. It helps if you get "let go" from your job and you get some form of severance pay; I formed Coates Consulting on the back of about six month severance.

As soon as the decision is made, you are working "24 hours a day". The first task is to establish the business officially, which might simply mean going to the local town hall and registering as a DBA (Doing Business as "your company"). This must be done. You may also set up the business entity and establish an LLC (limited liability corporation) or a corporation (most likely a Sub-"S" Corp if you are planning to file taxes as an individual). In the US, tax law, both federal and state, really tends to define how the business should be established.

If you have no plans to hire employees, at least in the short term, then forming a DBA or a simple LLC may be sufficient. In the latter case, companies such as LegalZoom provide a convenient service. The decision to form an LLC is an important one, and to some extent it depends on the nature of the business. Having the protection of a corporation (the corporate veil) can become

important in terms of overall liability - one can become exposed if something happens to a project, and there are financial repercussions.

If you are planning to form a good-sized consultancy you may want to form a partnership. This can be an LLC in which partners have a defined share in the business but file taxes as individuals.

The decision to add employees is a big one, not least because failure to take the proper registration steps can cost you later on. There is a lot more work and liability in maintaining the business and with health care costs and payment of a third party's (employees) social security, the financial burden is greater.

The loss of an infra-structure, that is, equipment (copiers, fax machines, water coolers, etc.) and people that help you "do stuff" can be unnerving. If you are a one-man-band, your role has expanded to include the shipping, mailing, coffee-making and janitoritorial functions. Some small companies make use of incubator centers where many of the infra-structure services are provided for a weekly fee. This can become more important if a group of professionals are involved and the company functions as a partnership. But if you start really small, then working from home can work, at least for a few years.

Functionally, Coates Consulting was set up in a few days after a couple of visits to Staples and Costco. Today's computers and home cable internet lines have made things a lot easier; with these and a professional-quality multifunctional printer you can appear as a good size business to the outside world. Some new businesses try to go 100% mobile, but from experience, a land line usually looks and sounds more professional.

Forming a consultancy

If you are a recognized expert in a particular technical field, the idea of becoming a consultant seems logical. But it is not necessarily easy to do. You need clients to get started… but for some reason they are not knocking on your door. You are now in the marketing or business development phase. You need a plan that combines what you are good at and what people need.

In my case, I formed an analytical business development service. I offered traditional analytical services if these were required, but the focus was on instrumentation and support of that business. I had experience in chromatography, spectroscopy and electrochemistry but was known as a spectroscopist, particularly optical spectroscopy (UV-vis, NIR, Raman and mid-IR). Consequently the company was formed with a focus on spectroscopy. Then, however, real life kicked in: the first two business opportunities were in chromatography (high speed GC) and mass spectrometry (non-optical), and they were for market development, not truly technology-based projects. I had to decide whether to go out of my comfort zone. I did, and both projects were successfully completed. That first check, no matter how large or small, is the most important. It sends the message, to yourself and the clients: I can earn an income consulting.

Today, 17 years later, 75 percent of the business is tied to spectroscopy and analytical chemistry, with the remainder being anything and everything within a general technology umbrella. Over the years I've included method development and instrument applications work (both hands-on and written application notes), as well as instrument concept development. Expanding to include hardware was a big decision, but it enabled other people to be brought into the business, in the form of contractors, without the need to hire additional staff. Pure consulting can be very limiting because you are constrained by what you as an individual can handle. Bringing on projects that can be handled by others is one way to expand the business. Another, to bring on partners or employees, is more complicated, and may result in you losing control of your time and ultimately of the finances.

Sustaining momentum

Once you've had some successes, where next? One option is to expand the scope of the business, but you must not lose direction or become overwhelmed by work. For any project, only about half of the allotted time is actually doing the work, the other half is taken up with managing the business. One has to become a master at juggling time, work and funds, and of doing so without it being obvious to the outside world. You must appear to be spending 100 percent of your time on each and every project, which is no mean feat.

Growing the business also requires that you get the message out. There are many ways to do this, requiring investment of time, money or both. Advertising is expensive, and not always effective. Writing in magazines is a good way to start. It takes time to write a good article, but it is typically a good investment. Other cost-effective strategies include the product directories of trade magazines, and press releases about the business, services and products.

In summary, make certain that you understand the basic rules of doing business. Hire additional expertise if you need help and use professional services to supplement what you do. Most importantly, hire a good tax accountant, they are worth their weight in gold. Finally, have confidence in yourself, even if times get tough; be prepared to multitask, and always have a plan "B".

John Coates in Principal at Coates Consulting, based in Newtown, CT, USA.

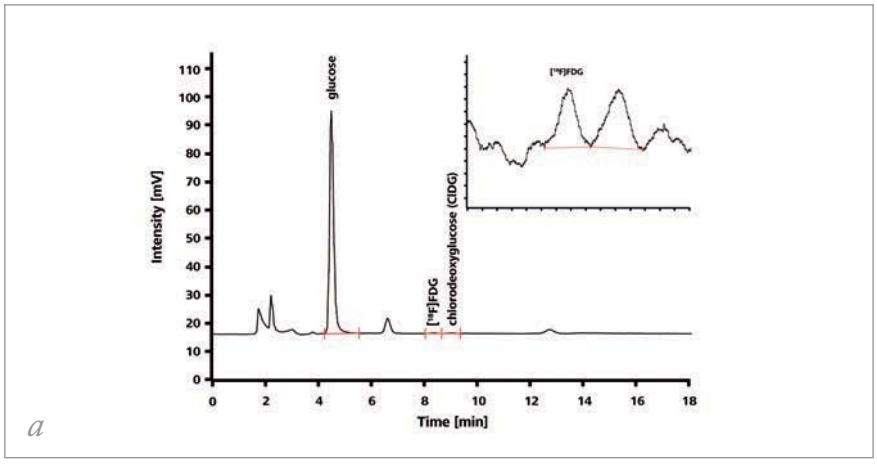
Hot Chemistry: Radio Ion Chromatography

Metrohm's highly customizable chromatography system copes with the tough requirements of the radiopharmaceutical industry and pharmacopoeial regulations. One single multichannel radio IC meets the quality control requirements of various production lines. Besides the high quality, the Metrohm IC presented here ensures users' safety, low maintenance costs, and outstanding ruggedness.

Radio IC aims to determine the radiochemical purity of radiopharmaceuticals. The latter are radioactive substances that are used for medical purposes, mainly in diagnostics, but also in the treatment and prevention of certain diseases. [18F]fluorodeoxyglucose and [18F]fluorocholine are two prominent examples of radiotracers which are used in diagnostics by positron emission tomography (PET). They are labeled with the radionuclide [18F] fluorine. During the radioactive decay of the unstable isotope, a proton in the nucleus of [18F]fluorine changes to a neutron. This process is accompanied by the emission of a neutrino and a positron. The latter combines with an electron in the surrounding tissue resulting in annihilation of both particles, and emission of two photons (gamma rays) in opposite directions, each with an energy of 0.511 MeV. From the data acquired through coincidence detection of the photon pair, the location of its emission in the patient's body is calculated. The latter coincides closely with the location of the original radiotracer molecule and thus reveals information on its activity.

The purity of radiotracers is of crucial importance. The highly energetic gamma rays emitted during the combination of a positron with an electron are harmful to the human body; by using pure radiotracer, i.e., by avoiding injection of free [18F]fluorine or other radioactive contaminants, the amount of radioactive substance administered to the patient can be kept to a minimum.

The quality control of the radiotracers is done by radio ion chromatography, in the short time between their synthesis and the recording of the three-dimensional PET scan. The separation step in radio IC is equal to that in regular IC – apart from it happening behind lead doors. What really sets radio IC apart from conventional ion chromatography is the detection step, in which a radioactivity detector is added to the setup. The radioactivity chromatogram reveals the presence of radioactive contaminants or, ideally, their absence.



(a) IC-PAD chromatogram with the glucose precursor, the carrier-free [18F]FDG, and the impurity chlorodeoxyglucose. (b) Radioactivity chromatogram of the [18F]FDG. The IC software converts the radiation units, counts per second (cps), to mV. Chromatographic conditions: column: Metrosep Carb 1 - 150/4.0; eluent: 0.1 mol/L NaOH, 1 mL/min; column temperature: 25 °C; injection volume: 10 µL.

VWR-Hitachi Chromaster with Diode Array and Low Temperature Evaporative Light Scattering Detectors (ELSD): Separation and detection of polyphenols in sage buds.

UV detection methods are the most widely used in HPLC owing to the seemingly ubiquitous presence of chromophores in analytes. However, not all analytes of interest are blessed with this property. ELSD is considered an almost universal, powerful and cost effective technique, and is ideal for the majority of liquid chromatography applications. Today, the power of this detection mode is further extended with a new model that introduces a genuine and efficient Low-Temperature technology combined with an innovative detection chamber, as a result providing the highest sensitivities for all compounds including semi-volatile and thermo-labile ones.

The Chromaster's 5430 Diode array detector is comparable to conventional ultraviolet (UV) detectors in noise with a value under specified conditions of 0.5 x 10^{-5} AU (or less). A variable air-volume fan and a specially designed cover on the spectrometer minimise the influence of temperature change around the optical system and achieves a drift value of 0.4 x 10^{-3} AU/h (or less) and a reduction in lamp stabilisation time by about 30%.

The sage leaf sample (2.0 g) was extracted twice with 15 mL of acetone using a homogeniser. The extract was centrifuged, and the residue was washed and agitated twice with 5 mL of solvent. The combined extract was evaporated to dryness under reduced pressure. The residue was dissolved in 4 mL of methanol and passed through a 0.45 µm filter. 20 µL aliquots were analysed by HPLC.

For more information: chromatography@eu.vwr.com. Or search for "Chromaster" or "Evaporative light scattering detector" at vwr.com

Time/s	*A%* (0.1% formic acid)	*B%* (Acetonitrile + 0.1% formic acid)
0.0	96	4
6.0	83	17
15.0	50	50
15.1	0	100
25	0	100
25.1	96	4
40	96	4

Flow rate:	0.8 ml/min
Run Time:	40 min including re-equlibration
Pressure:	130 bar
Oven Temperature:	20°C
Injection Volume:	10 µl
Column:	Merck Hibar® 150-4.6 mm Purosher® STAR RP-18e, 3 µm, Cat. No. 1.50470.0001

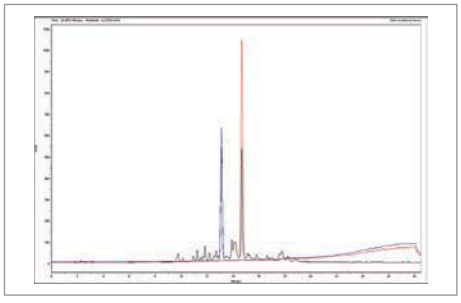


Figure 1: DAD trace at 330 nm (Extracted WL: 285 & 330 nm, Resp.time: 1s, Sampling.period: 400 ms, Slit: coarse, BandWidth 4nm) Sample: 10 µl of Sage buds extract 1:1 diluted (in 80% methanol)
Blue: Luteolin-7-O-Glucosid standard
Red: Rosmarinic acid standard

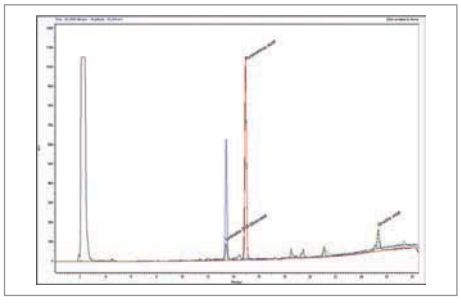


Figure 2: ELSD trace (Drift tube temperature: 50°C, Gain 10, Filter: 4s, Sampling rate: 200 ms- 5Hz, Auto-Zero)
Black: Sage buds extract (80% methanol) 1:1 diluted
Blue: Luteolin-7-O-Glucosid standard, 101 ug/ml
Red: Rosmarinic acid standard, 103 µg/ml
Green: Ursolic acid standard, 20 µg/ml

Lab-on-a-Sheep

Sitting Down with Sue Lunte, Ralph N. Adams
Institute for Bioanalytical Chemistry, Departments of Chemistry and Pharmaceutical Chemistry, University of Kansas, USA.

We have to start with that title. Do you mean it?

Sure, we are developing "lab-on-a-sheep". It started years ago at a talk by Jim Jorgenson on coupling liquid chromatography and capillary electrophoresis: I remember thinking, "Maybe we could use the same approach to couple microdialysis and capillary electrophoresis". Ten years later, things had been miniaturized and we took advantage by putting it on a freely-roaming animal. We can probe blood or the brain; our current project monitors neurotransmitters in the brain of sheep. Our goal is to simultaneously monitor neurotransmitters and behaviour, the latter using time-stamped video. So you can look for spikes in dopamine and relate it to the animal's behaviour.

It sounds like a project that will attract attention

We've had a lot of interest from people who study behaviour, but we've also had discussions about using the approach in hospital intensive care units to monitor people with traumatic brain injury – it has potential to be developed as a portable device to assess changes in neurotransmitter concentration. That summarizes what's really great about analytical chemistry: when you come up with something there's usually more than one application for it.

I am in charge of the Ralph (Buzz) Adams Institute. He went from fundamental electrochemistry to developing analytical instrumentation to look at neurotransmitters in the brain. He had a sign in his lab that said "Each scientist owes it to himself and to society to address the largest question for which the tools are ready and he is the right guy." We've put that in a prominent position in the Center because it's really important that researchers think about the impact of their work on the world.

Is that why Analytical Methods, for which you are Editor-in-Chief, requires authors to include a statement on societal impact when submitting a manuscript?

That was the decision of the editorial board. We wanted to differentiate ourselves from other analytical journals, and saw solving real-world problems as the way to go. Other journals can have the first demonstration of new techniques (often under very controlled circumstances); we are interested in the application of rugged techniques to real problems. It gives us a particular flavor. Actually, we don't publish the societal impact statements, but it might be a good idea.

Your career has been at the interface between chemistry and biology. Which are you?

I am a chemist. I was a chemistry major and, while I work at the interface, I see things from a chemist's point of view. The difference is in the attitude to quantitation: Chemists have a need to get at absolute quantities of things while biologists are trying to solve puzzles at the level of a system and are only interested in quantitation to the extent that it helps elucidate their system. Does it light up or not, that's what they want to know. The problems in biology are really interesting to me and it can be a lot easier to see the fruits of your labor as the work is often directly applicable to problems of health and disease.

When did your interest in science begin?

It feels that I've always liked it. I had good teachers; even at elementary school I attended nature club. I grew up in Detroit and my parents, who are not scientists, enrolled me in science courses at the Cranbrook Institute. At high school, chemistry was my favorite subject. What fascinated me was that it was so quantitative: if you took so much of one chemical and so much of another you could predict how much of a product chemical would be produced.

How would you assess the position of women in analytical science?

Things have changed over the years. When I was a grad student, only five or six of the sixty graduate students were women; today, our classes are more than 50 percent women. In the generation before me, a lot of the female professors of chemistry were single their entire life, they had to be married to the job. Now, you see a lot of dual-career couples, both faculty members. Things have gotten better but the fact that your Power List only had eight women shows that there is some way to go. Hopefully ten years from now, that will have gone up to 30.

Can you tell us about your Center of Biomedical Research Excellence?

COBRE grants are given by NIH to improve infrastructure and to mentor young faculty in states that receive lower levels of funding. Our center integrates analytical chemistry, engineering, molecular biosciences, and genomics through three core labs: microfabrication/microfluidics; molecular probes and model organisms; and next-gen sequencing. We have eight funded researchers who we are mentoring to apply for RO1 grants.

What are the advantages and disadvantages of being in a smaller academic institute?

It is different. We have a very collaborative environment that encourages interactions between scientists from different disciplines. Almost all my NIH grants are multi-investigator, including a biology expert, an instrumentation expert, and so on. The campus is not huge so it's easy for people to get together and work together. Egos don't get in the way too much here.

SHIMADZU
Excellence in Science

Qualities ahead-of-the-art:
the GC-2010 Plus

Excellence plus

The GC-2010 Plus not only tops the excellent quality of its predecessor model, but also adds new outstanding features increasing sensitivity, throughput, precision and separation efficiency. The Advanced Flow Technology (AFT) enables accurate flow control and excellent reproducibility.

- **MDGC – multidimensional chromatography analyzing complex matrices**
- **Backflush system and fast GC cut the analysis time**
- **Detector splitting for enhanced flexibility**
- **Detectors with market leading sensitivity**
- **Application-specific software packages providing complete solutions**

www.shimadzu.eu