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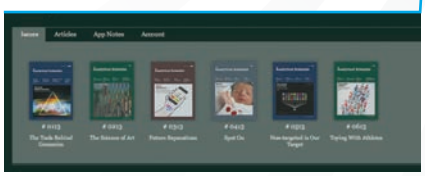

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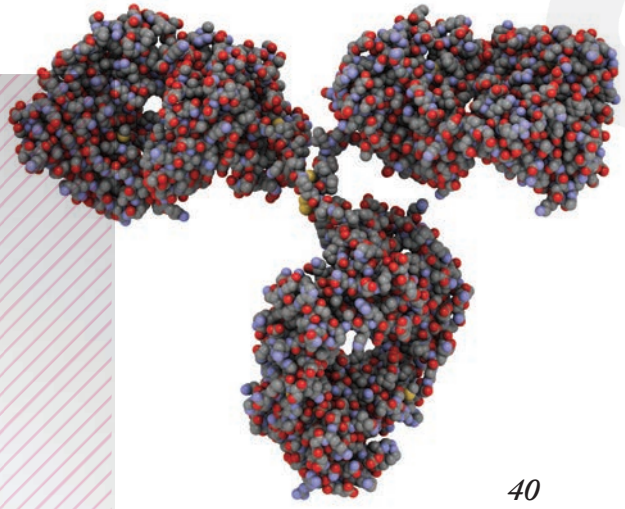

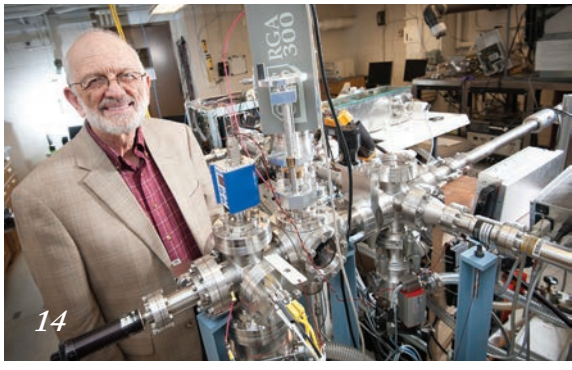

On The Cover

Mary Wirth features in a light pastiche of the iconic Che Guevara image created by Jim Fitzpatrick in 1968.

Upfront

In My View

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the **Analytical Scientist**

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The Accidental Guide to Innovation

As we prepare to launch The Analytical Scientist Innovation Award, the articles in this month's issue unwittingly form links in the innovation chain – from idea to marketed product – contributed by people who have been there, done that.

"Innovation is the application of new solutions that meet new requirements, inarticulate needs, or existing market needs," Wikipedia tells us. "This is accomplished through more effective products, processes, services, technologies, or ideas that are readily available to markets, governments and society."

That sounds pretty straightforward: it seems that we are all just one great idea away from an innovation. Actually, as some of you will know, successful innovation in analytical science bears an uncanny resemblance to the Olympic 3,000m steeplechase, with its 28 barriers and seven water jumps. It's a gruelling undertaking. Worse, you don't truly have an innovation until it has been widely adopted in the field, so the final giant hurdle isn't even in your own hands. Yet, innovation is the lifeblood of this field.

More by good fortune than by design, several virtuosos share their experiences in this issue. The patience and fortitude, as well as scientific brilliance, required of innovators shines through in interviews with mass spectrometrists Graham Cooks and Richard Smith, and in Mary Wirth's account of the development of submicrometer chromatography. Mary rightly acknowledges the importance of peer review – the sceptic-built barricade that stops lesser ideas in their tracks – and rightly concludes that simply observing something interesting isn't enough, you have to explain it too. Another imaginative innovation, the use of smart phones as biosensors, is described in the Upfront section.

Converting innovative science to innovative products is Neil Lewis' theme; the Bioscience Development Initiative is a bold new collaborative approach to developing tools that meet the analytical needs of the biopharmaceutical industry. Expect others to follow this lead. The drive behind pioneering developments is, of course, to increase effectiveness and to solve previously intractable problems. These are richly illustrated in Jaap de Zeeuw's discussion of selective GC stationary phases and in the transformative impact that acoustic liquid handling could have on drug discovery.

Our field is a hotbed of innovation. To recognize the most impactful, we are preparing to launch a search for the Top 10 Innovations in Analytical Science: submissions will be invited shortly. Watch this space.

Richard Gallagher
Editorial Director

Mark Hahnel

"I always wanted to stay in academia, but when I came up with a solution for a problem I had, something else took over..." says Mark Hahnel, founder of figshare, an open data tool that allows researchers to publish all of their data in a citable, searchable and sharable manner. Mark is fresh out of academia having just completed a PhD in stem cell biology at Imperial College London. "I'm passionate about open science and the potential it has to revolutionize the research community."

See page 16 for Mark's opinions on the current publishing model.

Mary Wirth

Mary Wirth is the W. Brooks Fortune Distinguished Professor in the Department of Chemistry at Purdue University. "I focus on new materials for protein separations," she says. "Applications include characterizing heterogeneity of protein drugs, top-down proteomics, and discovering trace protein biomarkers for screening of early aggressive cancer." Mary is a founding member of an independent national committee called COACh, which provides workshops for women all around the world who aspire to academic careers in science and engineering. Awards abound, and in 2014 Mary will be presented with the Dal Nogare prize for "contributions to the fundamental understanding of the chromatographic process".

For an account of slip flow and sub-micron separation, see page 28.

Jaap de Zeeuw

Jaap de Zeeuw's thesis was entitled "Fused Silica Capillary Column Technology" – the beginning of 34 years in GC capillary technology. Jaap has developed many PLOT and bonded-phase columns, and is also the originator of simple concepts for fast GC-MS using high vacuum inside capillary columns. "I've traveled widely and I am well known..." not only for his technical knowledge and teaching skills; Jaap has published more than 100 articles on GC column technology and applications.

Jaap urges chromatographers to be more selective on page 34.

Suwan Jayasinghe

"Inspired by many discussions with my father, I decided to move my research towards combining expertise in materials sciences with the biological and medical sciences in 2004". This move saw the discovery of both bio-electrosprays and cell electrospinning, which today are considered two frontline bioplatform technologies with, Suwan says, "a plethora of potential applications in biological and medical laboratories and clinics". Suwan holds a PhD in Materials Sciences, and has published over 130 scientific articles.

Read more about the potential of his research on page 18.

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Upfront

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

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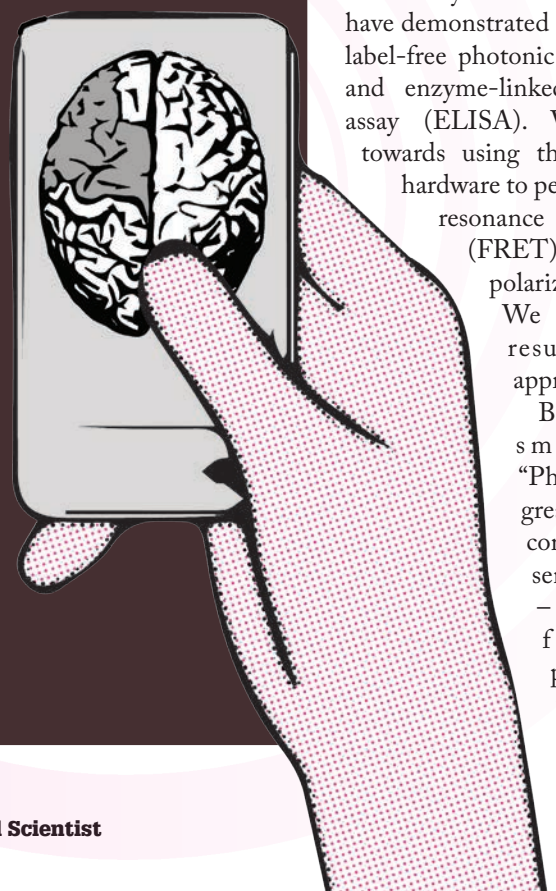

Smarter Smart Phones

A new biosensor cradle and app take us one step closer to portable and more universal analytical access

Researchers at the University of Illinois have developed a cradle accessory for the iPhone that aligns its integral camera with a series of optical components to analyze a primed slide. The result? A portable biosensing spectrophotometer that rivals a $50,000 laboratory instrument for accuracy, according to the team. In their paper in Lab on a Chip (1), an immune system protein was the main focus, but the sample slide can be primed for any biological molecule or cell type. Team leader Brian Cunningham tells The Analytical Scientist: "So far, we have demonstrated detection based on label-free photonic crystal biosensors and enzyme-linked immunosorbent assay (ELISA). We are working towards using the same detection hardware to perform fluorescence resonance energy transfer (FRET) and fluorescence polarization (FP) assays. We will be sharing results from those approaches soon."

But why target smart phones? "Phones have such great computational, communication, and sensing capabilities – it is now feasible for them to perform tasks that previously could only be performed by large and expensive laboratory instruments," says Cunningham. A single smart phone-based instrument is clearly not geared to high throughput analysis. Rather, the focus is on bringing detection to the sample or patient in environments that previously made analysis difficult or impossible.

"On the medical side, we started by thinking of assays for nutritional deficiency in remote parts of the world where there are not many doctors or diagnostic lab facilities," says Cunningham. "We have also been thinking of ways that people could more easily monitor the status of their health or the status of their treatment regimen through regular monitoring of a biomarker."

While medical applications are a tempting prize, Cunningham recognizes the regulatory hurdles (see "Smarter Administration", page 15). "I think that the regulatory path for medical applications can be expensive and lengthy, but fortunately there are many other applications that can be addressed. For example, detection of pathogens in food/water, measuring the protein or chemical contents of food or even of pharmaceutical source materials," he says.

So, how far from a portable biosensor in every pocket or purse? "In five years I think there will be inexpensive add-ons that will enable the most popular phones to perform analysis by using biosensor cartridges that contain the reagents and automate the assay protocol," says Cunningham. Moreover, the use of an intelligent app can provide detailed instructions to perform the assay as well as analyze and display the results. "I think such approaches will eventually gain FDA approval for certain applications. Apps will be able to share data with a Cloud-based data

How it Works

1. Functionalized photonic crystal fixed to standard microscope slide.
2. Slide placed into optical path of cradle
3. External broadband light passes through biosensor (resonant at only narrow band of wavelengths)
4. Diffraction grating spreads non-resonant wavelengths over smart phone camera pixels.
5. App displays photonic crystal's high-resolution transmission spectrum and calculates resonant wavelength with 0.009nm accuracy.
6. Slide exposed to sample and re-measured
7. The degree of resonant wavelength shift indicates amount of target molecule present in sample

Cost: $200
Analysis time: ~ 2 min per sample

management system to enable large-scale studies (for example, mapping the gluten content of the crusts from every pizza restaurant in New York City) or analysis of medical conditions by a remote physician. There are a huge number of potential applications," concludes Cunningham. *RW*

To see a video of the iPhone biosensor in action: youtu.be/Kh7MUjIYuyw

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1. *Dustin Galegos et al., "Label-free biodetection using a smartphone," Lab Chip, 13, 2124–2132 (2013).*

Monitoring Food Risks

A global, online risk-assessment tool offers a more intelligent way to protect against emerging food fraud and contamination – and provides a potential blueprint for other sectors

HorizonScan, a joint venture between a UK government group and industry, sources global recall, alert and food safety information on a daily basis, and categorizes it. "In managing food safety risks, the old adage of 'knowledge is power' is most certainly true", says Miles Thomas, Head of Knowledge Management at the Food and Environment Research Agency (Fera), which spearheads the project. The database is searchable by commodity, exporting country, issue, and, most importantly, risk.

The Analytical Scientist spoke with Deborah Jones, Fera Commercial Projects Manager, about the online tool.

Who?

"Fera spearheaded development, in partnership with Leatherhead Food Research, who provided additional development and commercialization of the tool."

Why?

"After the Sudan I illegal food dye issue, Fera wanted to develop a system that would provide early warnings. Customer feedback indicated that others would also be interested in such a system."

How?

"If you know what is currently being found in a commodity at a global level, it should give a better indication of what to look for at an individual country (or commodity) level. It also highlights the need to be aware that similar issues may occur in related commodities, for example, lychees and rambutans, or in the same commodity from a range of countries. Along with the current view, historical data enables you to understand if a particular issue – and therefore its risk – is increasing or decreasing."

Where?

"All reported contaminant issues are sourced from government bodies around the world – though they have no direct involvement in the project. The system is available worldwide and the global nature of the data makes it relevant for all."

Given the potential impact of HorizonScan's risk-based approach to global food safety, it may be time to consider similar models to get ahead of the game in environmental monitoring, illegal drug activity, or even anti-doping trends. *RW*

Risk assessment or better analysis? Let us know: theanalyticalscientist.com/issues/0713/202

Pre-diabetic Profiling

An integrated approach to uncovering distinct metabolite profile shifts in diabetes progression

The prevalence of type 2 diabetes mellitus (T2DM) is on a rampant rise across the globe, making it a critical area of study for metabolomics and biomarker discovery. The bad news is that the disease results from a complex interplay of genetic, metabolic, and environmental factors, complicating analysis. The good news is that progress is being made. Last month, we covered the molecular signatures of diabetic wound healing (1). Here, Choon Nam Ong, director of the Environmental Research Institute at the National University of Singapore, describes his group's recent research (2).

"The aim of our diabetes metabolite study was to investigate the potential of a metabolomics approach for the early detection of T2DM, even before the occurrence of hyperglycemia," Ong explains. His group's metabolomic platform technology allows assessment of a wide spectrum of metabolites, including fatty acids, carbohydrates, and

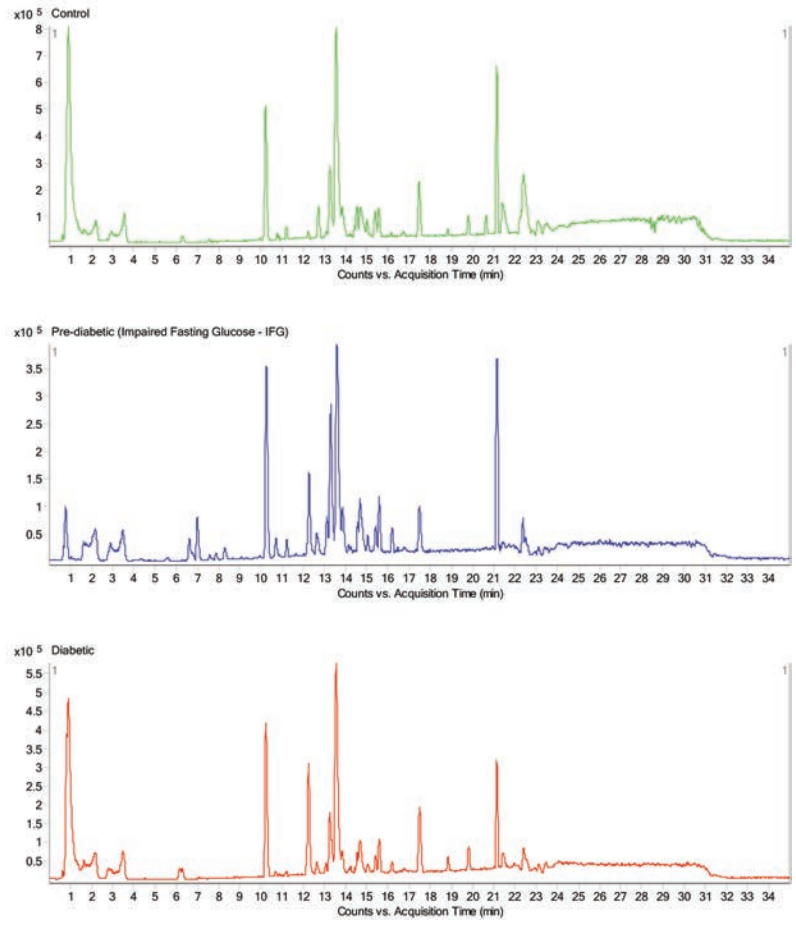

Fig 1 (Above): Base peak MS chromatograms of control, pre-diabetic, and diabetic samples indicate few defining differences.

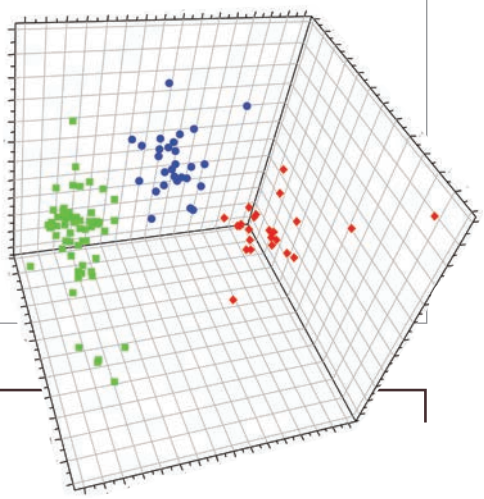

Fig 2 (Right): Multivariate analysis (OPLS-DA) shows that the three cohorts separate into distinct clusters.
■ Control ● Pre-diabetic
◆ Diabetic

The Experiment

Samples are assayed in parallel using GC-MS and LC-MS.

Systems:
Agilent 6890 GC system equipped with a 7683 autosampler and HP-5MSI fused-silica capillary column.

Agilent 1200 HPLC with an Agilent rapid resolution HT zorbax SB-C18 column (2.1 × 50 mm, 1.8µm). Agilent 6410 Triple Quad mass spectrometer, managed by a MassHunter workstation.

Data Analysis:
Spectral data were analyzed using orthogonal projection to latent structures discriminant analysis (OPLS-DA; program: SIMCA-P+ 11) to model predictors (variables/molecular ions) to responses (disease progression).

amino acids, that are closely involved in cellular physiology, structure, signaling, and disease onset. "Hopefully, this will offer better insight into the biological mechanisms of the early stages of metabolic disorders," he says.

The approach combines two chromatographic techniques (see sidebar, "The Experiment") to cover as fully as possible the numerous metabolic pathways likely to be affected. Ong explains: "The two techniques offer different capabilities for measuring a wide range of major biomolecules. For example, carbohydrates, amino acids and a large spectrum of fatty acids are detected using GC-MS, whereas many larger, less volatile molecules, such as sphingolipids and a wide range of phospholipids, are measured using LC-MS."

The strength of the study lies in the breadth of metabolites that can be measured and compared between healthy individuals, pre-diabetic subjects, and confirmed type 2 diabetes mellitus patients. The group obtained a large amount of spectral data from these three cohorts and used multivariate analysis (OPLS-DA) to observe three distinct clusters, identifying further metabolites that were markedly different between them using the "variable importance in the projection" values.

But Ong is already looking to build on the findings. "One main limitation was the small number of pre-diabetic subjects (24 out of the total 111 serum samples assayed). We are extending this to a larger cohort and also want to look into the temporal changes of the disease biomarkers," he explains.

Though Ong's group has already studied metabolite profiles of other diseases, such as asthma and cancer, this is the first time that they have included a non-clinic-based, community component – and the findings were not entirely expected. "The extensive metabolite shifts among the pre-diabetic subjects was certainly a surprise," he says (see Figure 1 & 2). "It suggests that subtle pathophysiological changes have already taken place in these subjects and that our integrated approach can be used for early detection of diabetes, which is of public significance." Regarding insights into the disease mechanism, Ong says that, "Our overall findings suggest that metabolic interplay between a number of pathways is associated with the development of diabetes." *RW*

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1. *theanalyticalscientist.com/issues/0613/201*
2. *F. Xu et al., "Metabolic Signature Shift in Type 2 Diabetes Mellitus Revealed by Mass Spectrometry-based Metabolomics," J. Clin. Endocrinol. Metab 98 (6) E1060-E1065 (2013).*

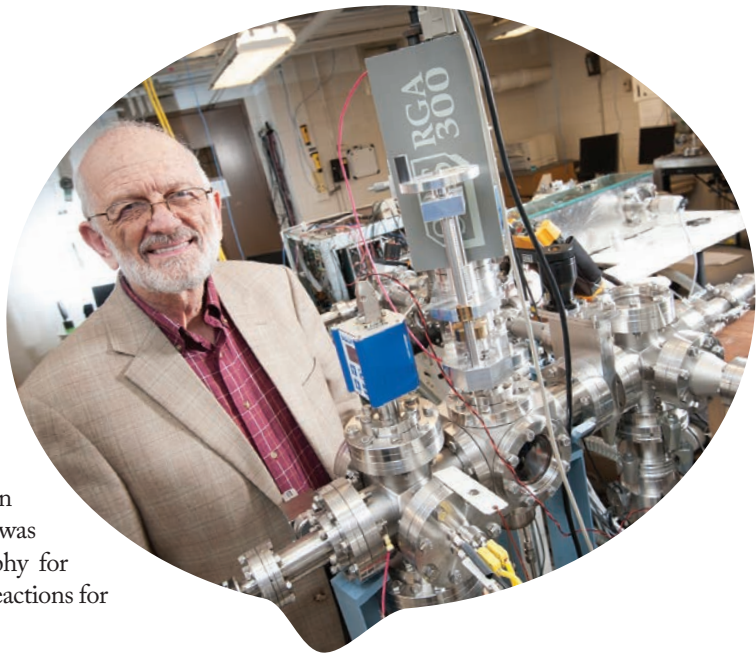
Mass (Spec) Approval

A discussion with Dreyfus Prize winner R. Graham Cooks

It has been a very good year for visionary mass spectrometrists. Richard D. Smith (see "Sitting Down With", page 50) was recognized for his Distinguished Contribution to Mass Spectrometry by the American Society for Mass Spectrometry, and R. Graham Cooks, Henry Bohn Hass Distinguished Professor of Chemistry at Purdue University, was recently awarded the biennial 2013 Dreyfus Prize in Chemical Sciences. The announcement from the Camille and Henry Dreyfus Foundation cited Cooks' introduction of tandem mass spectrometry, groundbreaking advances in ambient desorption/ionization, and his creation of miniature mass spectrometers. Here, Cooks discusses his career and his expectations for the future of chemistry.

Your reaction?
The subject for which I am being recognized has been decades in the making and many labs and individuals have contributed. I feel fortunate to have been part of this long-running campaign and to have experienced mass spectrometry when it was more a game with expensive toys and lots of promise, than a real science.

Your career?
That's a good story. I was in South Africa doing natural products organic chemistry (isolation, purification and structure determination, before spectroscopy was widely available) and doing pretty badly at identifying the alkaloids in my mangrove tree. Then Carl Djerassi of Stanford and steroid fame visited the University of Natal and gave a public lecture on birth control. I was chosen to give the student response and after a conversation he took a sample back to Stanford and sent the mass spectrum and the structure within 10 days. After that, it was hard to do chromatography for separation and chemical reactions for structure determination!



Your motivation?
I like the excitement of science, the emotional richness. I like that we don't know the answers and don't really have recipes for getting them (unless the questions are boring). So, the unknown – plus the examples of energetic and driven people whom I have known.

Your inspiration?
All my work goes back to simplifying the process of complex mixture analysis – this includes the MS/MS experiments on plant material and biofluids that we did in the mid-70s and the recent ambient ionization experiments and the attempts to do on-site measurements by mass spectrometry. The latter requires a miniature mass spectrometer.

Your recommendation?
I really like the work on single cells done by H. C. Chang's group at Academia Sinica – taking mass measurements out to 10^{13} Daltons. Also, the very elegant studies of Helmut Schwarz (Technische Universität Berlin) on catalysis in the gas phase. And I am a great admirer of Don Hunt (University of Virginia) who gets a major share of the credit for starting the field of proteomics.

Your inspirational words of wisdom?
Analytical science has great dynamic range. You can work on the practical end, on emerging instruments, or on big data manipulation. You can collaborate and publish with surgeons, with crime fighters, with the FBI/MI5, with biologists of all genotypes, and with your vet and pharmacist. High quality work can be done wherever you are and whatever your position.

Your predictions?
Ions are one of the states of matter. Given that there are only four or five such states, mass spectrometry – the science and technology of ions – should get 20-25 percent of science resource... More realistically, MS on every synthetic chemist's bench, monitoring reactions and intermediates in real time, including air- and water-sensitive reactions. To get to that point we should teach organic labs using mass spectrometers to run (solution phase) reactions on the one microgram scale (preparative MS) and go through substituent effects, kinetics, and solvent effects, in a single three hour lab period. At the end of the semester/term, real-time MS will be as essential to that group of students as NMR is now. *RW*

For more on the Cooks Group: aston.chem.purdue.edu. For more on the Dreyfus Foundation: www.dreyfus.org

Smarter Administration

The talk of TED but a few months ago, uChek, an iPhone-based urinalysis system, came almost immediately under fire from the FDA. There's an app(roval) for that…

"It has come to our attention that you are currently marketing the uChek Urine analyzer […]" began a foreboding letter from the US Food and Drug Administration (FDA) (1) to Myshkin Ingawale, co-founder of Biosense Technologies, India. Given that the iPhone, app, and urine dipsticks all come together for the qualitative and semi-quantitative determination of urine parameters (glucose, urobilinogen, pH, ketone, blood, protein, bilirubin, nitrite, leukocyte, and specific gravity), the FDA considers uChek a device within its jurisdiction. "Any company intending to promote their device for use in analyzing, reading, and/or interpreting these dipsticks need to obtain clearance for the entire urinalysis test system (i.e., the strip reader and the test strips, as used together)," warned the letter.

Ingawale is no stranger to TED or "devices". Back in February 2012, he unveiled another portable (non-iPhone-based) device to noninvasively measure the hemoglobin content of blood using photoplethysmography and reflectance spectroscopy. The aim? To "democratize healthcare" by preventing unnecessary deaths caused by anemia through simple, affordable tests placed in the hands of the health workers that need them. Things have gone very quiet on that project – several research papers on the same subject dating back to 2002 could indicate patent problems (2) – but it's hard to bemoan such noble intentions after watching his TED Talk (bit.ly/GCvNPp).

Going back to his latest uChek system, the app uses an iPhone camera to compare the dipstick results with a color mat (for lighting normalization), and provides information to help users understand the results – whether it be an indication of a kidney problem, urinary tract infection, hypertension, or diabetes complications. Certainly, plenty of scope to turn all iPhone users into hypochondriacs.

Ingawale appears to have a keen eye on the developing world, so the FDA letter is unlikely to dampen his entrepreneurial spirit. *RW*

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1. *http://1.usa.gov/Z2ghow*
2. *T. Aldrich et al., "Length-normalized pulse photoplethysmography: a noninvasive method to measure blood hemoglobin," Ann. Biomed. Eng. 30(10):1291-8 (2002).*

Open Science

Founded by frustrated student Mark Hahnel in 2011, figshare has blossomed to offer a cloud-based publishing solution to otherwise wasted research outputs

What?

Figshare allows researchers to publish figures, datasets, media (including video), papers, posters and file sets in a citable, searchable, and sharable cloud-based platform with unlimited storage space for publicly available data and 1GB of free space for secure private data.

Why?

Mark Hahnel realised that much of his research would never see the light of day in the traditional academic publishing model. As well as negative data, he had datasets, videos, and graphs that didn't help to make up a complete publication. So, he went about making some of his research outputs available online. For more on Hahnel's motivations, see page 16.

How?

1. Register for a free account at figshare.com
2. Login and 'Upload new' in 'My Data'.

Details

- Research data is published under Creative Commons license
- All publicly-available research receives a DataCite DOI on publication to aid traditional citation of non-traditional outputs
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- Security, persistence, and time-stamping of uploads make it easier to prevent plagiarism of research data
- Version control of all publicly available data is supported, and any privately stored data can also be altered or deleted. *RW*

For more information: figshare.com or follow @figshare on Twitter.

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

Open Your Science

Academia is fundamentally broken. You're wasting your time producing data that will never be published because the scientist down the hall didn't publish it either. Why aren't we more concerned?

By Mark Hahnel, founder of figshare, Digital Science, London, UK

There are very few, if any, discoveries each year in academia that come about without building on concepts and ideas that have been previously published in academic journals. That's how research progresses. Unfortunately, academics are rarely able to build upon actual research data, because it's not readily available.

Perhaps the most depressing part is the waste of research outputs. Significant funding and researcher time goes into performing experiments that produce null results or negative data. This doesn't need to be a bad thing. Researchers conduct experiments based on good prior knowledge of the field and a subsequent well-formulated hypothesis, but no single academic can be right all of the time. When we conduct experiments – often at great financial (and emotional!) cost – that do not confirm the hypothesis, what happens to the research data and results? In short, nothing.

Null results or negative data generally go unpublished. And while there have been some (largely unsuccessful) efforts to rectify this, a lack of true incentives appears to be holding things back. I'll freely admit that I wouldn't want to spend weeks of my own time writing up a paper based on negative data, only to see it rejected by most journals and have little to no impact – particularly with regards to my career. But I think this suggests the impact system and associated reward could be wrongly configured.

What is the benefit of making negative data available? Consider a scenario: 20 research labs carry out the same experiment with the same hypothesis, which proves to be false. Statistically, 19 of the 20 research groups come to the correct conclusion, but a five percent statistical significance margin yields a single group that obtains a false positive. In the current academic publishing world, this one false positive could be the only result disseminated. Moreover, if researchers base their own hypotheses on the published literature, they'll be wasting time and money building upon research tacitly proven to be false by the majority. Inevitably, this will produce further null results – or more false positives.

Great potential lies in the ability of subsequent researchers to make new analyses of the same data, including in combination with other data sets, or to use it in ways that had not been anticipated by the original author. Also of critical importance is the ability to reproduce published findings, which is difficult if not all information, such as raw or meta data, is available.

For a long time, researchers have understood that the currency of academia is publication. And the system is very well played by most academics: publish often in high impact journals, and you are likely to continue down the tenure track to success and prestige. There's nothing wrong with this to a certain extent. Peer review does act as a

reasonable filter for important academic advances, but it does not solve the other problems above. Luckily the system is changing. There are new incentives for researchers to make all data available. Funders are beginning to demand that all research outputs are made available. And companies like figshare are working with publishers like PLOS (Public Library of Science) to offer solutions at the time of publication. The way in which academic content is distributed around the world is changing. By making all research outputs available through open access and creative commons licensing, we can, as academics, really start building on the work of those before us. In the meantime, feel free to challenge colleagues who aren't pushing in the same direction! ■

"Great potential lies in the ability of subsequent researchers to make new analyses of the same data"

The Potential of Analytical Chemistry in Ghana

Every day, analytical chemists are making a practical difference to health and well-being. In our country, we face serious challenges in making this difference and the returns on a small investment in analytical science in Ghana would be enormous.

By D. K. Essumang, G, E. Adukpo and J. K. Bentum, Department of Chemistry, University of Cape Coast, Cape Coast, Ghana

Everyone faces challenges in their work, but perhaps we analytical chemists in Ghana face more than most. Government and private company laboratories typically have a reasonable range of equipment that may include gas chromatography/mass spectrometry, high-performance liquid chromatography (HPLC), Fourier transform infrared spectroscopy (FTIR), etc. However, Ghanaian universities lack most of this equipment and where it is available it is often not serviced, and is consequently unreliable.

Analytical chemistry involves qualitative and quantitative analysis; it requires the use of knowledge in chemistry, instrumentation, computers, and statistics to solve problems in almost all areas of chemistry. It is an important tool for helping to reveal the presence of harmful pathogens or substances in soil, air, drinking water and foods that have hazardous effects on humans and the environment. Since it is a service discipline, it combines the skills of a chemical analyst with knowledge of the unique problems of other chemical disciplines, such as organic, inorganic, and environmental chemistries. As elsewhere in the world, analytical chemists have a great deal to contribute to the health and development of our nation.

However, exact science requires specialized chemicals, materials, and equipment for sampling, isolating, and performing separations, for concentrating and preserving samples and for validating and verifying results through calibration and standardization. These processes are often costly and time-consuming. This is especially true when strict accountability and controls are necessary to meet regulatory requirements, and when a large number of samples must be analyzed for the minutest quantities of toxic pollutants. Equipment, such as freeze-driers, HPLC, auto-samplers, sonicators and SPE-cartridges, are not available most of the time.

The challenges faced by our discipline at the universities in Ghana are typical of institutions in developing countries. They include the acquisition and maintenance of basic and advanced

"The challenges faced by our discipline at the universities in Ghana include the acquisition and maintenance of basic and advanced scientific instrumentation and of chemicals."

scientific instrumentation and of chemicals. For example, we do have a Shimadzu atomic absorption spectrophotometer but we can't use it to measure water and wastewater quality. The basic reagents for measuring biochemical oxygen demand (BOD), dissolved oxygen (DO), even to assess conductivity, temperature, salinity, turbidity and chloride are limited or unavailable here. It limits the frequency of sampling as well as the number of analyses performed on a given sample. The absence of other modern equipment, such as gas chromatography systems or advanced mass spectrometers also makes research very challenging, compelling most analytical chemists to work on aspects of metal and pesticide analysis that might not necessarily be hot research topics in the developed world.

"We have the potential in Ghana to have a thriving little community of analytical scientists. We most certainly have the need for it"

Despite the drawbacks, we are still proud to teach new generations –

Creating and Analyzing Artificial Tissues

Two tissue engineering technologies, bio-electrospraying and cell electrospinning, provide realistic in vivo facsimiles of disease for high-throughput drug analysis.

By Suwan N. Jayasinghe, leader of the BioPhysics Group at University College London (Institute of Biomedical Engineering, Centre for Stem Cells & Regenerative Medicine, and Department of Mechanical Engineering), UK

Organ and tissue transplantation faces many obstacles. Not the least of these is the unwanted immunogenicity of the graft, which requires lifelong immunosuppressive therapy. This has side effects that can range from unpleasant to severe. To address this and other obstacles, one promising approach is decellularization–recellularization, in which biochemical approaches are used to tease cells out of tissues or organs, leaving behind the biological scaffold that is subsequently be repopulated with the recipient's own cells. This significantly reduces the need for immunosuppression and, while the technology is in its infancy, it is very promising. However, it shares a major stumbling block with regular transplantation, namely dependency on a donor pool that is heavily oversubscribed.

So, is there a good alternative strategy that bypasses the donor issue? I believe that synthetic tissue could fit the bill. It is another young but fast-developing concept that has already demonstrated significant clinical potential. Biocompatible materials can be formed into porous or fibrous scaffolds; these architectures provide a substrate for cell seeding, much like organs in the decellularization/recellularization process.

One goal of this approach is to patch damaged and/or ageing tissues or organs. In early attempts, the biomaterials used prevented cell infiltration throughout the entire scaffold and the cells only grew in two dimensions.

"Living cells, essential biomolecules, and a viscous biopolymer form true three-dimensional sructures"

To solve this problem, I have been applying bio-electrospraying and cell electrospinning. These techniques combine living cells, essential biomolecules, and a viscous biopolymer to form true three-dimensional structures that mimic native tissues and organs. By making use of a high voltage across electrodes, bio-electrospraying draws a jet that undergoes breakup to form cell-laden droplets for pinpoint placement in three-dimensions; cell electrospinning

hundreds of analytical chemists yearly. Indeed, analytical chemistry applications are among the key tools used by most students in research at undergraduate and post-graduate levels. Unfortunately, here, we again face an equipment problem: it is over-stretched to service the large numbers of eager students.

We have the potential in Ghana to have a thriving little community of analytical scientists. We most certainly have the need for it: continuous environmental monitoring is a must here, as in all developing countries. The process of monitoring itself, and the incorporation of analytical findings into risk management decisions, is dependent on assumptions and procedures. In many cases, these assumptions and procedures are dynamic and can have large impacts on outcomes. With the right analytical equipment (we already have the appropriate know-how), we could be making a huge difference. ■

creates a continuous cell-containing fiber that forms a scaffold. Both approaches mimic three-dimensional native tissues, allowing cells full access to nutrients.

We have performed in depth in vitro and in vivo studies of bio-electrospraying and cell electrospinning in mouse and rat models, and we are currently engaged in challenge trials in pigs and sheep. Many fully functional tissue types, such as skin, muscle, cardiac, and brain, have been generated in sheets or vessels. These contain multiple cell types and a whole host of biomolecules to enhance selected features, such as vascularization and wound healing.

"Our bioplatform research offers great potential in an analytical or diagnostic setting."

Although the original focus of our bioplatform research was the construction of three-dimensional synthetic tissues for repair, replacement, or rejuvenation, it offers great potential in an analytical or diagnostic setting. In fact, we are investigating the potential of cell electrospinning/bio-electrospraying bioplatforms at a smaller scale for high-throughput applications. Tissues of a specific type – for example, cancer or otherwise disease-specific tissue – is fabricated at the millimeter scale in a 96-well format, enabling rapid screening of targeted small molecule therapies against experimental, clinical, or genetic criteria, for example, age-related and/or hereditary diseases.

The progression from in-vitro models (functional assays) to in-vivo systems that more closely mimic disease is an exciting one and will provide fundamental analytical insight into many aspects and therapeutic targets that were previously beyond study. The analysis of three-dimensional tissues in massively parallel studies will provide insights on disease progression and translational implications (for example, wound healing). And by using genome sequencing and subsequently identified at-risk organ biopsies, patient-specific tissue arrays could be created for drug screening or even discovery with a view towards personalized medicine. ■

Cracking the Epigenetic Code

Mass spectrometry (MS) approaches are increasing our understanding of how DNA is regulated in real life.

By Pawel Olszowy, Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, USA, and Department of Environmental Chemistry and Bioanalytics, Nicolaus Copernicus University, Torun, Poland.

Everyone knows the genetic code. Not so well known or understood is the epigenetic code, which sits on top (literally and figuratively) of the genetic code. While all the cells of one organism share a genetic code, the epigenetic code, consisting of different types of modifications that impact the genetic code, is unique to every cell.

Within the nucleus, double-stranded DNA helices are wound around proteins called histones to form nucleosomes, which can be compared to a thread wrapped around a spool. Post-translational modifications (PTM) to the N-terminal end of the histone proteins direct the maintenance or remodeling of the nucleosome structure and can have positive (activating) as well as negative (repressing) effects on the regulation of transcription. The profile of histone PTMs is known as the epigenetic histone code for a particular cell, and is a subject of increasing research interest.

MS offers an alternative approach to epigenetic research. The more typical way to detect and identify post-translational modifications of histones is Western Blot. However, this technique requires specific antibodies, which do not exist for new modifications. Using mass spectrometry, all kinds of modifications – known and previously unknown – can be identified. By adding appropriate molecular mass to the precursor ion, post-translational modifications can be identified manually, or the entire process can be determined using proteomic software.

No mass spectrometer stands out as being the best fit for epigenetic research. In fact, it is best to combine fragmentation techniques to gain a comprehensive list of post-translational modifications. As an example, we have used fragmentation data collected from collision-induced dissociation (CID) and electron transfer dissociation (ETD) techniques. Using CID we detected nearly all of the reported acetylation on lysines of the Histone H4 proteins. With ETD, which is a more subtle technique, we identified ubiquitination and phosphorylation modifications, none of which were detected using CID.

Comparison of the LTQ Orbitrap XL (Thermo Scientific) and TripleTOF 5600 (AB Sciex) mass spectrometers showed that one major difference between them is sensitivity. Slightly more modifications were found using TripleTOF but the number of identified modifications using LTQ Orbitrap XL could be increased by applying ETD. If I had to choose a single instrument, I would go for one that allows more than one fragmentation technique. Even though this compromises sensitivity a little, more modifications are identified in comparison to instruments of greater sensitivity that rely on a single fragmentation source.

The MS approach to proteomics does have some weaknesses. One is protein identification. While we can analyze many samples with very good resolution and sensitivity in a short period, the software currently available to study posttranslational modifications and quantitative proteomics is lagging: it takes several times longer to perform a search than to analyze a sample. This computer/software bottleneck will be one of the major problems for companies to deal with.

"The MS approach to proteomics does have some weaknesses. One is protein identification."

A second issue is performing quantitative/comparative proteomics. Many methods have been developed, such as stable isotope labeling with amino acids in cell culture (SILAC) and post-labeling during sample preparation for mass spectrometry analyses (that is, isobaric tags for relative and absolute quantitation (iTRAQ) and ^{18}O). Despite the fact that these methods allow quantitative proteomics, there are question marks over their precision and accuracy.

Reports of new post-translational modifications are an almost daily occurrence, so it is unclear when the full epigenetic code will be known. More important, however, is the assignation of functions for these modifications because it is on this knowledge that new targeted therapies can be developed. These will be based on appropriate modifications, on inhibitors and on enzymes, such as histone deacetylases. A complication is that this new range of therapeutic options will have to be delivered to the nucleus. ■

Slip Flow Star

The use of submicrometer particles in chromatography, viewed as heresy when first suggested a decade ago, is today seen as a possible quantum leap in separation efficiency. This is a first-hand account of the origins of the idea, the experiments that yielded crystal-clear data and the literature on slip flow that provided an explanation of the remarkable findings.

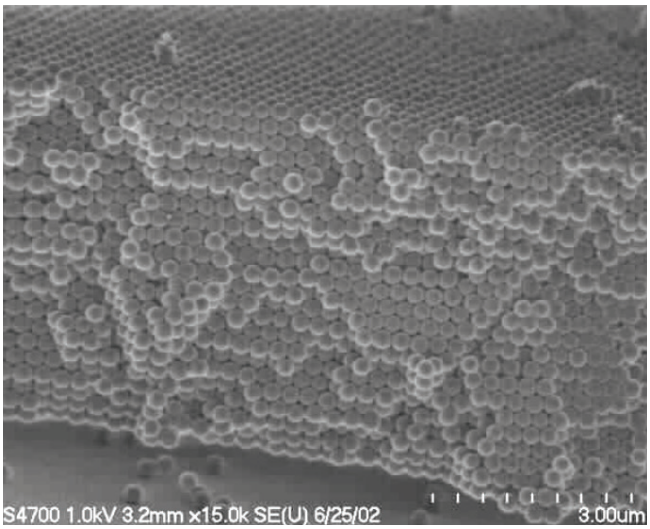
By Mary J. Wirth

The -omics era has inspired creativity across analytical chemistry by posing interesting new challenges. In my case, the stimulus to think about new materials for separations came at the 1999 Gordon Conference on Analytical Chemistry, which included the emerging field of proteomics. I was taken aback by the images of stained two-dimensional gels, which are riddled with streaks, especially for large proteins, and wondered why no-one commented on these and how they must hide lower abundance proteins. When I asked, people said "that's just the way it is". The gel images made me think about what kind of material could enable protein electrophoresis without streaks.

Around the same time that proteomics was emerging, photonics had become a hot topic in physics. A photonic material strongly filters out a narrow band of light by using diffraction instead of absorbance. In 2001, I read a paper on silica colloidal crystals, which are made of submicrometer silica particles. When the sizes of these particles are on the order of the wavelength of light, diffraction occurs in the visible part of the spectrum, imparting color. In fact the beauty of gem-quality opals is familiar to everyone, and these are silica colloidal crystals that occur in nature. To show what caught my interest in the paper, Figure 1 shows a scanning electron microscopy (SEM) image obtained later from our own lab, as well as a photo to demonstrate that the material has color. What jumped out at me from the SEM image was the extraordinary homogeneity. I saw this as potentially the ideal separation medium. The holes between the particles are the right size for electrophoresis, and the size of the holes can be varied by varying particle size. The streak problem should be solved because there are no small pores that would trap proteins. They might even be useful for chromatography. These thoughts motivated me to start studying silica colloidal crystals.

I was at the University of Delaware at the time, and I convinced a brave graduate student that these materials were worth working on. We bought the necessary reagents and started to make the silica particles, and then we formed silica colloidal crystals on microscope slides. The university had just acquired its first field-emission SEM, which allows imaging of non-conducting materials, and my student became skilled at operating it. She coated some slides and took the SEM image in Figure 1; I snapped the photo. We were on our way.

We quickly got pretty good at making these materials, and I wrote a proposal to the National Institutes of Health (NIH) to study protein electrophoresis. Usually these stories end with the reviewers being so skeptical that the proposal was declined, but that did not happen in this case. The NIH study section thought the risk was worth taking, and the research was funded. But there was an odd wrinkle: one reviewer was apparently so struck by the beauty of Figure 1 that he or she said we could not have done it ourselves. Hey, thanks for the vote of no confidence there. Anyway, I got a phone call from the NIH misconduct office asking me about the origin of the image. I explained that we made the material and we imaged it. I think they realized the reviewer had simply made a careless comment, giving no basis for the claim that the image came from elsewhere. We got the funding, so we were able to start in earnest. I will be forever grateful to the supportive reviewers for taking this risk. We published the first electrophoresis results for these media, using DNA fragments to confirm that the pores enable sieving. We have done quite a bit of electrophoresis in the years since then, and indeed, there are no streaks because proteins are not trapped. We will develop many more applications of protein electrophoresis in the future, but the story now turns to liquid chromatography (LC).



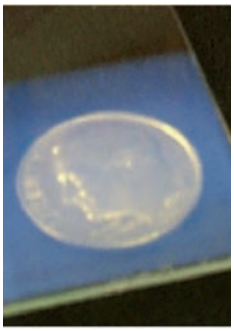


Fig 1. (Top) Field-emission SEM image of ordered film of silica spheres (200 nm) prepared in our lab in 2002. This is a side view of cleaved sample that was 4 μm thick. (Right) Photograph from 2002 of a typical microscope slide coated with silica colloidal crystal from the same particle size. The blue color is from Bragg diffraction, and the dime behind the slide shows that these materials are optically transparent. Reprinted with permission (1).

Plate height sensation

When we started working with these materials, I never imagined that we would someday be using pressure-driven flow through silica colloidal crystals. Geologists consider opals to be nonporous rocks. The crystalline structure is so tightly packed that it ought to take enormous pressures to flow liquid through it. But we were curious about how the material would perform in chromatography, so we started doing electrochromatography of proteins. This uses electric-field-driven instead of pressure-driven flow, differing from electrophoresis by allowing the protein to reversibly adsorb to the surface. We learned to pack capillaries well, after a few years of fighting cracks and wall gaps.

The electrochromatography results were amazing: in 2010 we published a van Deemter plot in Analytical Chemistry (2) revealing that diffusion was the only contribution to plate height. The minimum plate height was about 10 nm, orders of magnitude smaller than anything ever seen for a chromatographic medium. The contribution to broadening from the material was zero, with an error of about 5 nm. This means that the material is indeed extraordinarily homogeneous.

"A surprising twist in the course of doing the electrochromatography work was that we learned we could flow mobile phase pretty fast through the silica colloidal crystal."

A surprising twist in the course of doing the electrochromatography work was that we learned we could flow mobile phase pretty fast through the silica colloidal crystal. How we started on this avenue was that we wanted to see whether our material would accidently slide out of the capillary since we were using no frit. A collaborator on the US east coast had a pump that went up to 12,000 psi, and she used methanol to test flow rates for a few of our capillaries. One capillary blew out the packing, but the others held up to the maximum pressure, and they gave consistent pressure-flow curves. She found that she could easily get enough flow for stable nanospray. This was significant because it indicated that one could potentially use silica colloidal crystals for LC mass spectrometry (LC-MS). Since the flow behavior was incidental to the electrochromatography paper, we put it in the supporting information and mentioned it in the context of future significance. I had no idea how important this seemingly minor point was.

There used to be a detective show on TV decades ago with a character called Lieutenant Columbo. He always found a seemingly minor piece of evidence that was the key to unraveling the murder mystery. Science is much the same way, and this is why reviewers will sometimes zero in on what might look like a minor point to you as an author. In this case, the late Uwe Neue of Waters was Lieutenant Columbo. He calculated that our flow rates were impossibly high. He was right, the high flow rates pointed to the material being loosely packed, but our SEM images established the material was packed tightly. We exchanged several emails, agreeing that the behavior was perplexing to both of us. Neue published a commentary on our paper in which he proposed that the beautiful crystalline structures one sees in the SEM images are only on the outside, and that the material was randomly packed inside (3). This was a reasonable conjecture, but we wrote a response pointing out that we see crystalline domains when we cleave the capillaries. An illustration of what we typically see in the lab is presented in Figure 2 and Figure 4. Our own conjecture was that there must be enough vacancy defects to support a higher flow rate (4). We were both wrong, but it would be a while before we figured this out.

We bought a high pressure pump and began to investigate protein ultrahigh pressure liquid chromatography (UHPLC). We expected that the plate heights would be much worse with pressure-driven flow because theory predicted that the smallest possible plate height was equal to the particle diameter. We were using 470 nm diameter particles, so we expected to observe 470 nm plate heights, at best. Instead, we were in for another surprise: the plate heights were an order of magnitude smaller. One protein gave a plate height of only 15 nm. This was 30 times smaller than theory predicted. Whenever we get a really surprising result, as long as it is reproducible, I tell my students this: the good news is that we learned something important, the bad news is that it will be a dogfight to get it published, no one will believe it.

We submitted the work for publication in 2011, and it was soundly rejected by all three reviewers. We spent a considerable time revising it to address the extensive comments and questions by the reviewers, and we re-

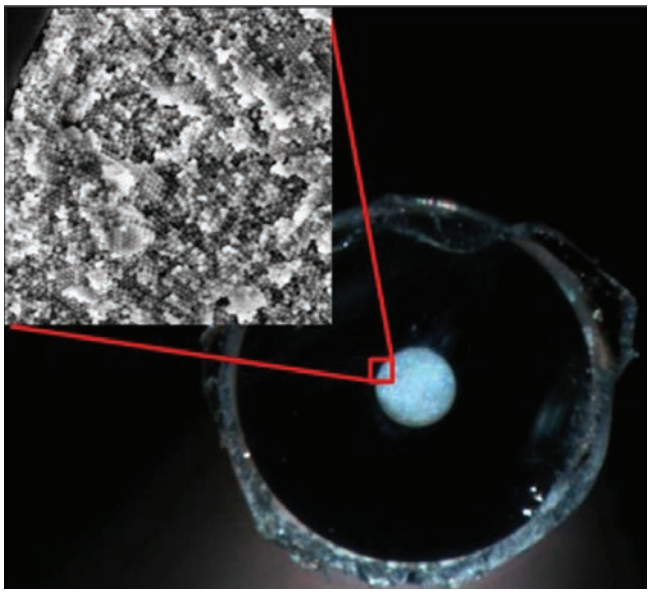


Fig 2. Photograph of a 75 μm inner diameter (i.d.) capillary with end-on view, showing opalescence from crystalline domains. The inset gives the SEM image of the same region of the capillary. Image is adapted and reprinted with permission (5).

submitted it. It was rejected again. The associate editor told me he never wanted to see this work again. There were two main problems. First, the small plate heights were so much smaller than theoretically impossible. Second, the flow rate indicated random packing, just as it had for methanol in our earlier work, yet the photo of the capillary exhibited the opalescence that you would only get with crystallinity. These two results made no sense. One reviewer suggested that we selected results from very different capillaries and pieced them together as though they were from one, violating ethical practice. I took great umbrage at the time, but I can see now that the reviewer was just trying to find an earthly explanation for the contradictory results.

In retrospect, I probably would have rejected the paper, too, if I were a reviewer.

Identifying slip flow

We would soon figure out what was going on with the plate height and flow rate.

My students were distressed about the paper being rejected after all of their hard work. Being older, I do not get as upset anymore. I told them that a correct new result will eventually see the light of day. I decided to relax and do some general reading. You may have noticed how your mind always works on a problem, even when you are not conscious of it.

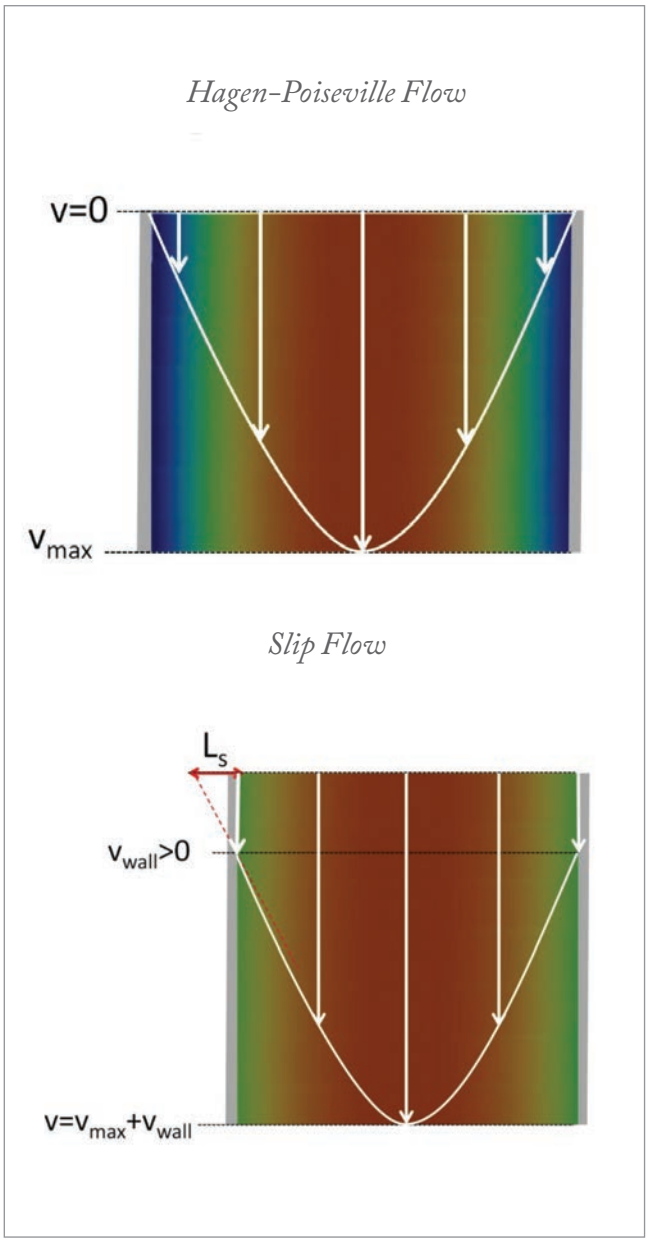


Fig 3. Contrast between Hagen-Poiseuille flow, which has conventionally been used in liquid chromatography, and slip flow. The velocity of the mobile phase is depicted in false color, showing that the velocity goes to zero in the case of Hagen-Poiseuille flow, but is nonzero at the wall for slip flow, giving a faster average velocity. Slip flow is described by the geometric parameter of slip length, L_s, which increases as the liquid becomes more non-wetting. For chromatography, the narrower color distribution for slip flow illustrates the narrower distribution of velocities that lower the plate height. Image adapted with permission from the Journal of Separation Science.

That was the case for me. I dug up a paper I had read a few years earlier and had filed it away as a curious observation. It was the 2005 paper in Nature by Majumder et al. (6) about something called slip flow, which enables high flow rates of water through carbon nanotubes. Slip flow is explained in more detail a little later here, but for now the essential idea is that slip flow enhances the flow rate when a surface is poorly wetted by a liquid. I instantly realized that slip flow might be responsible for our anomalously high flow rates, and possibly even our low plate heights. I was excited, but before jumping out of my chair and running to the lab, and perhaps needlessly alerting my students, I read a few other papers. Our interstitial dimensions seemed right for slip flow. Since our surfaces were chemically modified with hydrocarbon chains, it occurred to me that we could design an internal check: compare the flow rates for water and toluene, since one is nonwetting and the other wetting. I emailed my students a copy of the Nature paper and stated my new conjecture.

After reading my email message, one of my graduate students leapt up and ran into the lab to make flow rate measurements. He quickly had the answer: we had slip flow. The flow rate for water was five-fold higher than that predicted from the flow equations used for chromatography, while toluene matched the prediction. Slip flow thus explained why a tightly packed crystalline medium would give the same flow rate predicted for a looser, random packed medium when the non-wetting acetonitrile and methanol solvents were used. We wish Uwe Neue had lived to hear the answer to his question about why our flow rates are so high. Slip flow also offered a possible explanation for our very low plate heights since it flattens the parabolic flow profile of the mobile phase. We revised the paper to include slip flow results, and submitted it to a higher impact journal. It was accepted as a Journal of the American Chemical Society (JACS) communication without drama (5).

Slip flow is actually an old topic in fluid dynamics. I believe the first paper was published in 1823 by Navier (7). This early paper explains that you have a choice when you predict the flow rate: you can have the velocity of the liquid be zero at the wall, which is what has been used conventionally in chromatography, or you can have it be nonzero, which is what characterizes slip flow. These two cases are illustrated in Figure 3, where the color code depicts the spatial distribution of the velocity of the liquid. Slip flow describes your non-stick frying pan, where the fried egg slides out in one piece when you tilt the pan. In chromatography, where the mobile phase is equivalent to the egg, having all of the liquid move at one uniform velocity makes chromatographic peaks sharper. From the Navier paper, the information needed to understand our high flow rates and low plate heights has been there ever since Thomas Jefferson's day, we just had not made the connection.

We followed up with a paper in ACS Nano (8) on the particle size dependence of slip flow. We included multiple internal checks: my graduate student made a total of over 200 measurements: three replicate capillaries for eight different particle diameters, with at least five measurements of flow rate for water at various pressures, and the same for toluene, for each capillary (he was a high-energy graduate student). The data confirmed that slip flow enhancement increases as particles sizes decreases, in accord with theory. The results also detailed that the particle sizes used commercially in chromatography give almost no slip flow, which explains why most chromatographers had never heard of it.

"Slip flow also offered a possible explanation for our very low plate heights since it flattens the parabolic flow profile of the mobile phase."

A few months ago, Xiaohong Yan and Qiuwang Wang published a theory paper in the Journal of Separation Science (9) that starkly disagrees with earlier theory on plate heights, predicting the minimum plate height to be more than ten-fold smaller than the particle diameter, even without slip flow. Our smallest plate height was less than a factor of three smaller than their prediction. Had they published this a few years ago, our own adventure in publishing might have been much less interesting. Maybe they would be the ones who had the interesting ride.

We now understand why the flow rates and plates heights were out of the range of what was thought to be theoretically possible a year ago. Using the work of Yan and Wang, the current state of knowledge is that the plate heights for proteins can be <50 nm, with most of the improvement arising from the unusually small particle size coupled with the homogeneity of

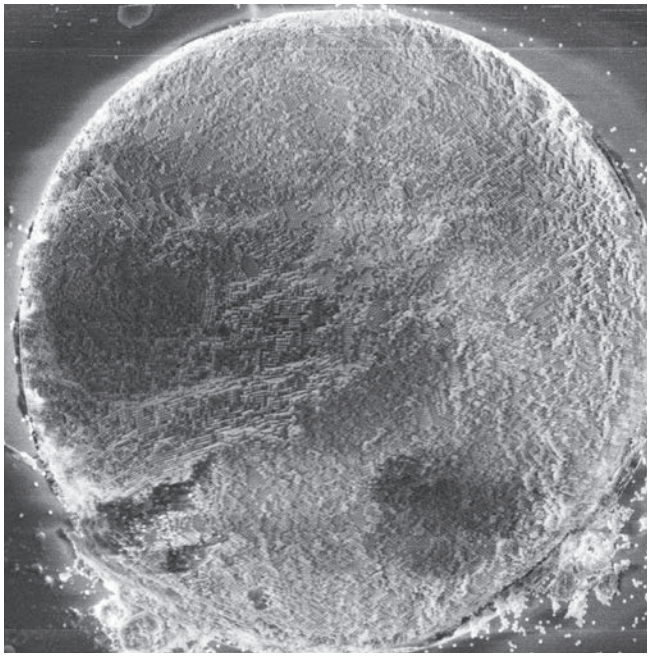


Fig 4. SEM image of full capillary cross-section, with 470 nm particles.

the medium, and part of this arises from slip flow. I would say that the main role of slip flow is to facilitate the use of such small particles with currently available LC pumps.

Directions

Our published work on chromatography with silica colloidal crystals was initially artisanal: students electrokinetically injected protein, then put a pressure fitting on the capillary, hooked it up to a high pressure pump, and detected the protein peaks by fluorescence microscopy. These are slow, laborious steps, and we undertook them to image the injected width, to make sure it was small. Now we are using a nanoUHPLC with an autoinjector to reduce labor and increase throughput, and the system has a dual pump to enable the gradient elution needed for protein separations. The first paper using this approach, just accepted by Analytical Chemistry, shows that there is not too much penalty with the broader injection from the commercial instrument. We are now ready to explore applications.

There are three areas we have identified where better chromatography of intact proteins ought to have a significant impact: proteomics, protein pharmaceuticals, and biomarker discovery. We are preparing our first paper on proteomics by nanoUHPLC-MS of intact proteins. The chromatograms are a far cry from the streaky and slow gel separations, and the in-line integration with mass spectrometry allows the type of automation not possible with gels. For protein pharmaceuticals, where there is a pressing need to characterize aggregation of monoclonal antibodies, we show baseline resolution of monoclonal antibody monomers from their dimers and trimers at room temperature in only a few minutes. No other separation has come close to this resolution or time scale, even at elevated temperatures. For biomarker discovery, we are picking up on leads where LC was used, but the resolution was insufficient. Overlapping peaks can undermine biomarker discovery by masking lower abundance proteins that are changing between healthy and disease states. We are evaluating studies of various cancers and cardiovascular disease.

When I was young and full of new ideas, I was inspired by stories demonstrating how the discovery process is so different from scientists yelling "eureka" from the laboratory. These stories explain that when you observe something strange, your peers expect you not just to report it, but to explain it. That is where the science begins, and it will lead you into interesting new directions and take you way out of your comfort zone. Once you are out there, you get to experience what it is really like to be a scientist.

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As a lab manager, how can you boost vitality, promote collaboration and engender inspiration among your staff? Here, Gregory Weddle describes how lab design can enhance the creative process while Bill Devorick proposes that personal mindfulness and an understanding of motivation theory will improve teamwork. Combine these to create your own 'Maximum Lab'.

Designing for Discovery

Laboratory design can be conducive – or unconducive – to creativity and productivity. Can today's lab layout and rationale, a legacy from 60 years ago, be improved upon? I say yes, and go back even further in the history of the laboratory for inspiration.

By Gregory Weddle

While the range of equipment has expanded dramatically over the years, the laboratory's raison d'être is the same as it was in the days of Gregor Mendel (1822-1884), Thomas Edison (1847-1931) and Alexander Fleming (1881-1955): experimentation. The lab provides the setting for scientists to observe the world and test the postulates of inspired minds in a repeatable manner. Walking through Thomas Edison's lab in Michigan a few years ago, I wondered how he repeated anything at all. His main tools were his eyes, sketchpad, scales, and calipers; and most measurements were taken by devices invented by Edison or his technicians, leveraging math and science. Yet the basic structure required of his and other illustrious researchers' workspaces is mirrored today (see sidebar, "Laboratory use").

The in-silico lab equivalent in Mendel's time was his desk: an oil lamp, paper, quill, and ink well. Bookcases were filled with every written reference he could get his hands on. His mind was the only computer he had at his disposal to decipher, in minute detail, his expectations and observations. For his free-thinking lab, Mendel had pots, calipers, a scalpel, some dirt and peas to test and prove his theories or, in some cases, to convert a chance or tangential observation into a new concept. In his campaign lab, Fleming worked on increasing mold harvests, proving and reproving concepts, and improving safety, purity and effect.

Mendel, Edison and Fleming were inspired to wonder: "What if?". How do we nurture that spirit today, and can the lab configuration contribute to it? My role is to work with clients to discern the needs or goals for a space, then to influence the design to most effectively support those goals. Whether the target is volume output, or an environment to capture perception, expression, or conception of thought that can lead to the creative processes (see Figure 1), we need to understand the impact of space on people.

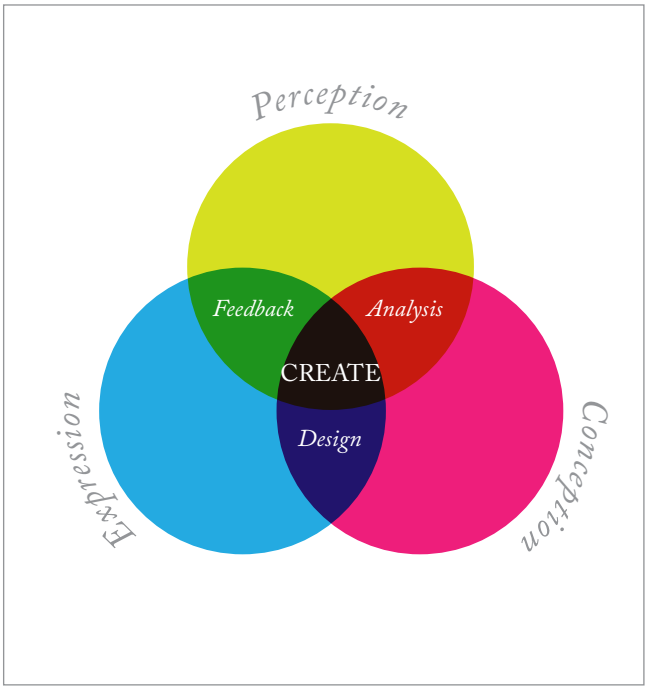

Fig 1: Understanding creativity. Adapted from "How the Creative Process Works", by Robert Lindsay Nathan, Ludwig von Mises Institute, 2009 (mises.org/daily/3461)

Understanding the creative process

Lab space, historically and today, is fashioned by the room available and what scientists had at their disposal: instruments, hand tools, assistants, desks, chemical and biological materials, power, gases, water, and so on. Safety was, at first, an individual responsibility; today we have engineers, architects, and environmental health and safety professionals looking out for our well-being.

The traditional lab of today was conceptually designed in the 1950s and 60s following academically-guided constructs. It provides us with the familiar stark environments and cramped storage, often with no thought for optimized or integrated technologies. Avi Hofstein and Vincent N. Lunetta's work points to the lack of innovation in laboratory design in the academic

Laboratory use

In-Silico: Supports computerized modeling and analysis. Provides access to or contains the computer systems, desktop office/work areas, and collaborative space.

Free Thinking: For testing theory or converting chance observations into invention. Often a typical wet lab with support for a range of instrumentation.

Campaign: For testing and charting characteristics of identified compounds. Designed to move discovery as far as Phase I clinical trials.

Production: Supports production with assay tests, or for manufacture of products for development use.

Quality & Compliance: For testing of final product for potency, consistency, structure integrity, stability, etc.

Laboratory configurations

Open Lab: Typically houses specialty analytical instruments for use by multiple scientists, leveraging investment into key instrumentation. Requires high instrument uptime, easy instrument setup, teardown, cleaning and validation.

Flex Lab: Allows configuration changes based on scientific need without implemention of a complex facility modification project. Variable in the degree of flexibility, but normally allows basic movement of furniture and utilities.

Traditional Lab or Wet Lab: Constructed for a broad range of desktop experimentation. Designs are based on repetitive workstations of utilities (water, gases, waste path), and the safety of scientists. Majority based on classroom laboratory configurations from the early to mid 20th century.

Lab Use						
In Silico	Open					
Free Thinking			Flex			
Campaign		Flex	Open			
Quality / Compliance					Traditional	Flex
Production				Traditional		Open
	Chemical	Biochemical	Automation	Tissue Culture	Analytical	Development
Scientific Focus						

Table 1. Lab Categorization. See sidebars "Laboratory Use" and "Laboratory Configurations" for defnitions.

environment and how those designs drove commercial lab spaces for the next 50 years (1). The pharmaceutical boom of the 1980s and 90s delivered millions of square feet of lab space following these outdated precepts.

Sadly, the creative process is imperiled in such environments. It is somewhat ironic that Big Pharma actually contributed to the lack of facility innovation as they attempted to create their own campuses and labs to reflect academic campus and labs, all with the idea of attracting new scientists to a familiar environment…

So, how do we design an environment to better support the creative process? Well, lab layouts and work areas must provide places to engage in each of the three phases of creativity: environments that support perception, conception and expression. That means providing the opportunity to draw on existing technologies, connect with other researchers and access information so that we don't have to start from scratch; leveraging previous research; and offering a new view of the challenge. Therefore, work environments need to include the "wet lab" as well as "collaborative" and "contemplative" spaces.

Categorizing and designing

Just as the lab suite needs to support the creative process, we must also understand the design requirements of the wet and in-silico lab components. Much of the need here is defined by the phase and nature of the research. Chemical, biochemical, tissue culture, analytical and development research needs

must all be clearly defined and documented. Further considerations include any need for open access and flex labs, and the requirements of workflows and instrumentation. Documentation of these needs, provided by scientists, the processes themselves, and instrument manufacturers must be integrated to achieve the optimal solution. Instrument providers tend to sell a single instrument and its capabilities; however, it is rarely a single instrument that determines the output or success of research. We must consider the impact of all instruments, technologies, and consumables within the workflow.

Table 1 categorizes various types of lab space. By adding area or percentage of total space, lab planners can begin to understand how a lab functions with respect to lab activities, needs, and current organization. This table can also be used to assign available space to the types of science that would be best suited to it.

Communicating the value, features and limits of a new lab to those who will use it is all-important. For example, the flex lab may be perceived as being "adjustable to every need" but in reality it is simply designed to deliver flexibility for a targeted set of conditions. A scientist who believes they can move fume hoods around to meet their need for the day may be disappointed or even put in danger if the "flex" is limited to power and location of gases and drops.

We ask scientists to document their design targets and test them against user needs. This requires that they fully understand the new technology, collaborative tools, instruments, and features that they need. We discuss the intent of the entire suite, and relate each space to the creative process. Finally, we make sure that they know that it has been done to enable them to get the most out of their research efforts – and to be inspired!

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Striving with Intention

Understanding the motivations of your staff through the combination of mindfulness and motivation theory can help you improve teamwork and boost the vitality of your staff.

By William D. Devorick

Analytical laboratories can be stressful places. Management wants steady output at lowered cost. Production customers require results to release product. Quality assurance demands compliance with high standards and strict documentation. And the complexities of science and instrumentation do not always yield to analyst intentions.

Almost any analytical laboratory can improve in terms of motivation, teamwork, vitality and fun. But how can an engaged manager bring these changes about? I suggest 'striving with intention' as one way, by which I mean applying motivation theory in a mindful fashion. Here, I shall introduce the concept of motivation and describe mindfulness, and explore how they can be used together to improve the working dynamic in the laboratory and the overall success of the team.

The process starts with you, the manager. To have a positive impact on laboratory dynamics, you must first care for yourself and want to improve your personal awareness; you must pay mindful attention to your experiences, to the realities of the environment, and to improving your analytical and critical thinking abilities. You must also care for your team. And you must have concrete tactics.

In a review of decades of motivation research, Vallerand (1) concludes that the extent of motivation (or passion) is determined by a combination of factors: the person, the job-at-hand, and the social setting. Motivation theory in the context of mindful attention, provides a solid basis for problem-solving that is relevant to the analytical laboratory.

Motivation theory

The history of motivation theory is storied. Reeve (2)

developed the concept that there were three 'grand theories' in the early study of motivation. The first, the theory of will, dates back to Socrates, Plato and Aristotle. The will intervenes in decisions related to wants and needs, guiding the decision to either do or not do something. The second, the theory of instinct, has its basis in the ideas of Charles Darwin. In this view, biologically-based instincts, like those for food and comfort, direct behavior. The third, the theory of drive, has a focus on urges and their fulfillment, and found a supporter in Sigmund Freud.

Interesting as they are, these grand theories have been relegated to the back-burner as they are insufficient to address the practical realities of motivation.

A wealth of new theories arose in the second half of the 20th century that provided insights applicable to the workplace, such as achievement motivation theory, goal setting, flow theory and self-determination theory (SDT). To illustrate the practical utility of these concepts, I will give a synopsis of each theory and an example of its application.

Achievement motivation

Having both classic and contemporary interpretations (3), achievement motivation research shows that people in teams act with greater intention when they perceive their role as central to success (4). Similarly, each individual's orientation toward success, for example expecting to succeed or expecting to fail, influences his or her choice of tasks. So – and this is a common theme and starting place – careful consideration of each individual in the team is critical. Know yourself and your analytical team members, and your tasks and task complexity, then consider the team makeup and the perspective of each team-member on the tasks at hand.

Goal setting

A ubiquitous activity in businesses today, people seem to better accomplish tasks when they have goals and when the goals and tasks are properly challenging for each individual. Watch out for overly-ambitious goals, as these may indicate, counter-intuitively, a fear of failure.

Flow theory

Getting in the flow of activities and maintaining focus is an experience that most analytical scientists have while working in an area of competence on just the right challenge. Notice flow and energy levels in the laboratory, as these provide clues for successful adjustments.

Quick six to improve motivation

Develop mindfulness: Explore tools/techniques to improve mental function. A good start is Zinn's Wherever You Go, There You Are (6). Continue or start a meditation practice. Know personal limits and patterns of clear and less-than-clear thinking.

Know yourself: Observe the self. Use meditation and other tools, and know your own skills, strengths, and weaknesses. Improve competence and stay current with technical and interpersonal skills.

Know others: Discover the 'career' goals and skills of each individual. Work with others and maintain relatedness. Create a skills matrix. Trust each person to achieve his or her goals. Pay attention to verify progress and help out, as appropriate, to develop the competencies needed for the individual to continue to be a valuable contributor.

Know the team: Focus on the work at hand and listen to the sub-text. Pay attention to the level of confidence and expectations of each member. Consider mini-teams of two or three (for example, match a good teacher with somone lagging behind). Consider the cumulative capabilities of the team and match them to the challenge at hand. Foster communication.

Prime for success: Help others learn how to be successful. Be the one to clear obstacles or point the way forward. Appreciate the work being done. Understand the value of success, and failure. Monitor progress and make adjustments. Communicate.

Be fair and honest: Act with mindfulness and integrity. Fairness does not mean indentical treatment of each person. Be honest by relating helpful information and sharing skills, techniques, and understanding. Blend mindful awareness with analysis.

Self-Determination Theory

With the advent of the multiplicity of theories, a need for integration emerged. SDT seeks to integrate a variety of perspectives; Deci and Ryan (5) describe it as a macro-theory. In brief, STD posits two primary and two secondary categories of motivation. The primary categories are autonomous and controlled; autonomous motivation has the characteristic of 'self-endorsement' while controlled motivation is essentially extrinsic, either depending on rewards or punishments or on internalized schemas. The secondary components are relatedness and competence, highlighting the importance of knowing team member goals and individual outlooks to properly align these with the team's challenges. Luckily, in the analytical lab there are plenty of opportunities to be challenged and to enjoy making decisions. Aligning tasks so that each team member is intrinsically motivated, appropriately challenged and in the 'zone', can strengthen team collaboration and bring energy to the workplace.

I encourage managers to investigate motivation theory. A personal synthesis of theoretical ideas is a valuable tool for getting the best performance from yourself and your staff.

Mindfulness and inspired motivation

Zinn (6) describes mindfulness as 'having to do with being in touch'. A person's ability to improve his or her own mind, simply by attending to the mind as a functioning object in its own right, can be something of an eye-opener! This mental improvement is not just a felt sense, it also correlates to real neurological changes. Bringing active attention to the mind, that is, meditation, is the main way people develop mindfulness (see Figure 1). Direct observation of our physical experiences, feelings, and thoughts, fosters direct insight into the nature of our sense of self, releasing vitality, and supporting a stronger sense of our place in the world – and in the analytical laboratory.

The initial 'strangeness' of mindfulness has waned considerably in recent years. Conferences such as Wisdom 2.0 and the work of US Congressman Tim Ryan, for example, demonstrate the widespread interest in mindfulness as a way to improve health and effectiveness in the workplace and in society at large. With wide-ranging benefits chronicled in hundreds of articles, mindfulness is truly becoming a mainstream perspective and can be just the meta-skill needed to mobilize the right actions for improving the workplace.

Personal development is at the heart of mindfulness. Gaining personal understanding is the starting point and it can be introduced into teams, for example through group mindfulness training. This approach can instill a sense of community but it should be introduced on a voluntary basis, with no coercion of any kind. A casual, off-site group may be formed, spanning several departments of the workplace or multiple workplaces. A short set of four one-hour workshops, for example, can provide a starting-point.

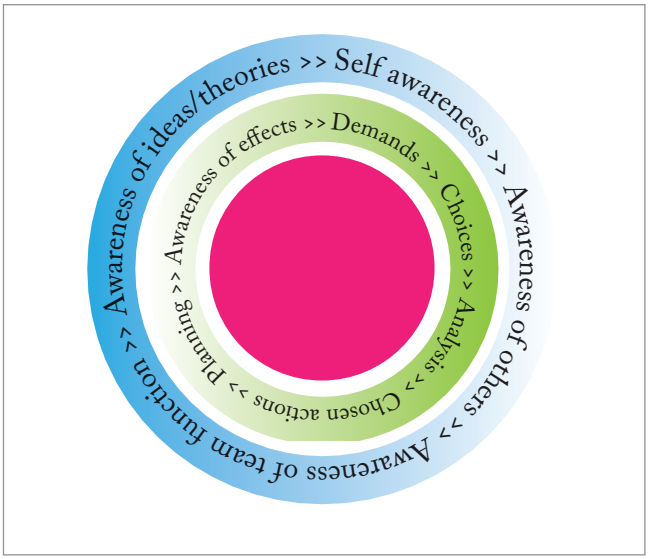

Fig 1. The circular nature of mindfulness.

The challenges of the analytical lab will not disappear. But with appropriate focus and attitude you and your team can perform better, with more vitality and greater enjoyment

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Get Selective

Modern narrow bore columns have made chromatographers lazy when it comes to stationary phase selection. Here's how getting back to the basics in gas chromatography by using selectivity can address challenging separations and reduce analysis time.

By Jaap de Zeeuw

Today's laboratories have to deal with an increased number of samples; throughput is a progressively more important factor. Solutions have been presented, for example, highly efficient narrow bore columns. However, operating 0.10 mm ID columns demands specific instrumentation and skills. Moreover, use is limited by sampling, loadability, durability, and the measurement of "fast" peaks. The use of 0.15/0.18 mm ID capillaries has been better accepted.

Selectivity is one of the "forgotten" factors affecting separation in gas chromatography. In the early days, when packed columns were the standard, many types of stationary phases were used to optimize separation because only 5000-10,000 theoretical plates were available. A selective stationary phase simply had to be chosen. With the introduction of the capillary column, selectivity became less important: by using 30-meter columns, over 120,000 theoretical plates are easily generated. Ditching selectivity for plate number translated into generalized phase recommendations, with only a polar (polyethylene glycol) and a non-polar (polydimethyl siloxane) type capillaries covering the majority of separations.

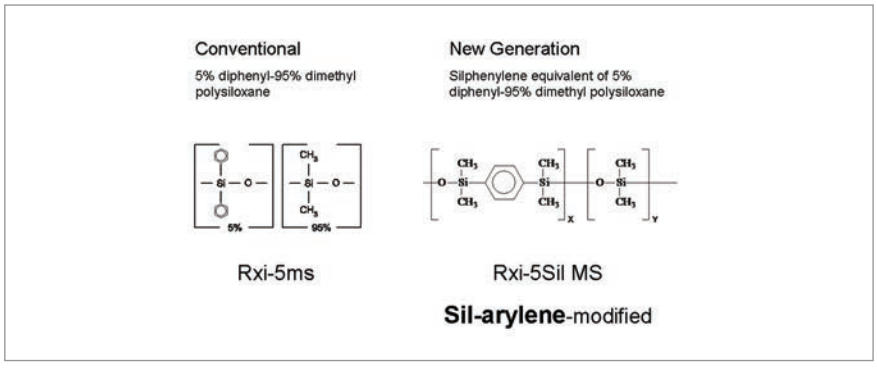

Fig 1. Structure of most popular phases (left). By incorporating the phenyl group in the chain, the phase becomes more thermally stable. However, the selectivity is also changed.

Even today, the majority of separations can be performed with only two phases (polar and non-polar), but, crucially, if faster analysis is also required, it is essential to approach the challenge in the right way.

Selectivity is your friend

One of the best ways to reduce analysis time is to use the selectivity of the stationary phase (see "Back to Basics" on page 36). As the selectivity factor has the biggest impact, a small change translates into a big difference in the separation of target analytes. And by using highly selective materials, shorter columns can be used, resulting in faster separations. For the fastest analyses, one can use the best of both worlds: selectivity and small diameter columns. Furthermore, selectivity can be manipulated by temperature (see sidebar "Manipulation of selectivity" on page 37).

Which stationary phase?

It was the first thing that my teacher taught me about selectivity: the most selective phase is the one that looks most like the

components you are analyzing. Initially, this appears a little strange; interactions will be similar for all component types, so how can I achieve separation? While true as an initial, general rule – separation is achieved by the size (molecular weight) of the component – in reality, the goal is to achieve a difference in retention based on molecular interactive forces that determine solubility. Such interactions are based on dispersion, formation of hydrogen bridges, van der Waals forces, dipoles, and steric hindrance. The best way to change the forces above is by using functional groups in the stationary phase that show maximal interaction with the analytes. Alcohols separate the best on a polyethylene glycol type phase and hydrocarbons will do well on non-polar phases like squalane or polydimethyl siloxane.

Over the last decade, we've made big breakthroughs in stabilizing stationary phases using silphenylene groups. We found that it was possible to reduce the breakdown reaction of diphenyl siloxanes by building the phenyl group in the main chain (see Figure 1) (1). Such phases show lower bleed, but also show different selectivity – something that is not always made clear by vendors – which can lead to strange examples of peak elution shifts; that's why some vendors supply traditional 5% diphenyl siloxane alongside the stabilized silphenylene phase.

For certain applications the silphenylene-stabilized phase offers better separation. Figure 2 shows the separation of aromatics on both phases under similar conditions and dimensions. The silphenylene-stabilized phase shows a separation of para- and meta xylene, while the 5% phenyl phase is unable to resolve the peaks. This is interesting as the separation was only possible using polar PEG and TCEP type phases. With more complex samples, there will be greater differences; we have seen issues with many compound classes (2-4). Modification of the backbone can do a lot for specific separations and several unique phase chemistries have been developed based on this premise for dioxins, chlorinated pesticides and PCBs, for example.

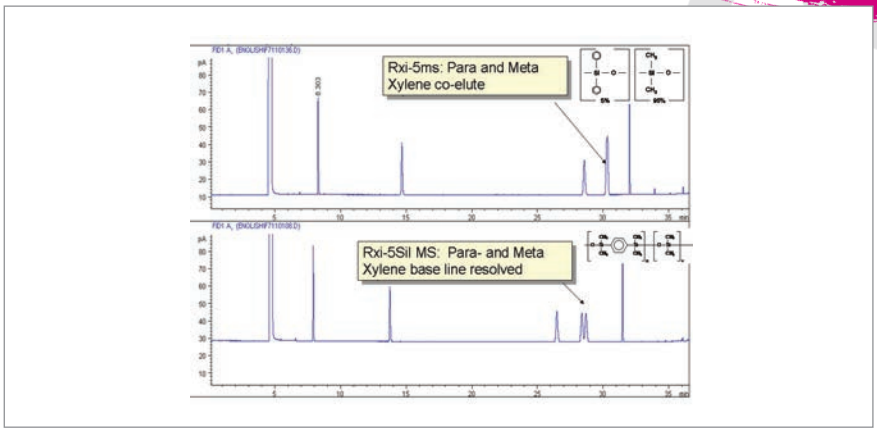

Fig 2. Separation of aromatics on a 5% diphenyl (top) and a silphenylene stabilized equivalent. Column: 60m x 0.25mm with 0.25 µm films; Oven: 30 °C; Injection: split.

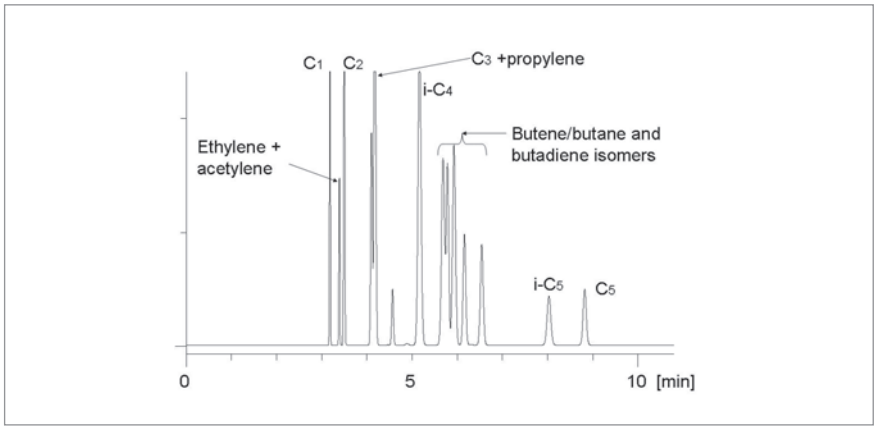

Fig 3. C1-C5 saturates and unsaturates on 100% polydimethyl siloxane. Column: Rtx-1 60m x 0.32mm, df = 5µm; Oven: 60 °C (5 min) > 10 °C /min to 175 °C; Carrier: H_2, 2 mL/min; 23 psi; Injection: split.

Light hydrocarbons

For the separation of light hydrocarbons, a phase with high retention and selectivity is required. The most selective phase for hydrocarbons is squalane, but it cannot be deposited in sufficiently thick films to generate enough retention. The second choice is 100% polydimethyl siloxane – the methyl groups ensure good interaction with hydrocarbons and film thickness of 5 µ can be easily achieved on 0.32mm ID capillaries. However, if 100% dimethyl siloxane is unable to resolve unsaturated hydrocarbons (as is the case in Figure 3), more selectivity is required and adsorption chromatography becomes an attractive option. Alumina interacts with hydrocarbons in a unique fashion, which allows complete separation of C1-C5

Back to basics

Here is the (simplified) resolution equation:

$$R_s = \frac{1}{4} \times \left[\alpha - 1\right] \times \left[\frac{k}{k+1}\right] \times \sqrt{N_{th}}$$

Resolution (R) between two compounds depends on plate count (*Nth*), retention factor (*k*), and the selectivity factor (α), but their relative impacts must be put in perspective.

Increasing k

Increasing *k* will only be of interest if k is very low as R increases and then near linear with increase of *k*. At higher *k* (longer retention time), the *k*-term becomes "1", meaning no additional contribution to R. The k of an existing column can be changed with temperature. k can also be changed using a column with a different phase-ratio.

Increasing Nth

Increasing plate count will always impact R, but the contribution is not large (square root value); a 4x longer column is needed to get 2x increase in resolution. Additionally, retention times are increased, making analysis time longer, and peaks broader and therefore lower. Longer columns also have a higher cost.

Increasing α

Increasing the selectivity factor will increase resolution linearly. The best way to optimize any separation is to choose the most selective stationary phase.

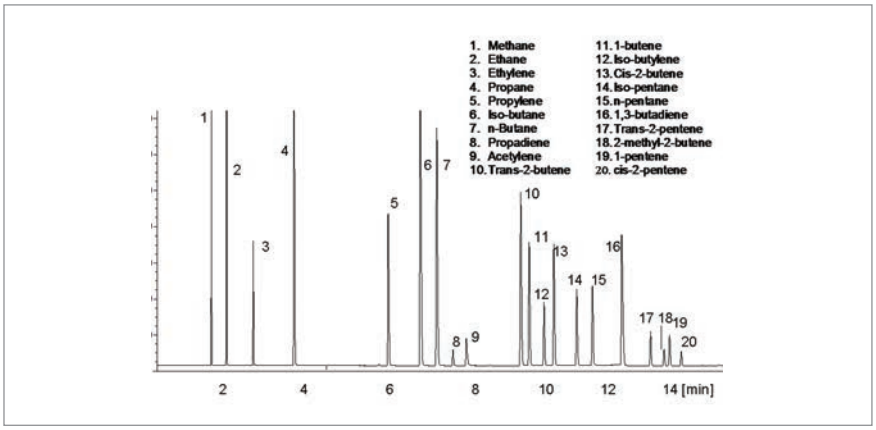

Fig 4. Ultimate selectivity for C1-C5. Rt AluminaBOND / Na_2SO_4; Column: 50m x 0.53mm, df = 6 µm, Oven: 45 °C (1 min) > 10 °C/min to 200 °C (3.5 min), Carrier: H_2; 8 psi; Injection: split. Detector: FID.

hydrocarbons at temperatures above 60 °C (see Figure 4). Furthermore, the high selectivity means that the analysis time can be reduced to a minimum using high linear gas velocities and high-speed programming.

Polycyclic aromatic hydrocarbons (PAH)

PAHs must be analyzed at low levels and elute at higher temperatures, so a low bleed system is required. The Silphenylene technology as previously discussed provides very stable solutions. Figure 7 shows the baseline resolution of all 16 traditional EPA 610 PAHs using a Silphenylene stabilized phase on a 30m x 0.25mm capillary. Benzo(g,h,i)perylene elute at 310 °C on a straight baseline.

However, the last ten years have seen more demand for measuring an increased number of PAHs, particularly in food analysis. In fact, the new list of current interest to the European Food Safety Agency is quite challenging – several isobaric PAHs must be quantified, which is not only a problem for flame ionization detection but also for mass spectrometry. Chromatographic separation is essential. Specific examples are the separation of benzo-fluoranthene isomers and the separation of chrysene-triphenylene. Increasing the Silphenylene content (for example, as in Rxi-17Sil MS, see Figure 8) increases selectivity for PAHs and provides the highest possible signal-to-noise ratio for trace monitoring; however, it does not offer enough selectivity for the separation of triphenylene-chrysene. Separation of triphenylene-chrysene can be obtained on a Rxi-XLB phase, but only at the expense of fluoranthene separation (5).

A new selective phase for PAH

At Restek, we recently developed a new high temperature phase that incorporated groups that specifically interact with both target PAH structures, which separates all relevant PAHs (see Figure 9), is stable up to 360 °C, and was found to be robust for repeated injections of PAH extracts from food. Dibenzo pyrene elutes at 350 °C; note the stable baseline at this very high temperature.

Manipulation of selectivity

Although selectivity of a stationary phase is a "fixed" parameter, it is also a function of the temperature. Changing operating temperature will affect the relative position of components in chromatograms; sometimes separations improve, sometimes they get worse.

For adsorbents, the stationary phase acts more "polar" when the elution temperature of components is reduced, which means that polar components elute later at lower temperatures. This effect is of particular interest with alumina columns, where polar hydrocarbons like acetylene and propadiene can be positioned before or after the n-butane peak, just by changing temperature conditions. With a 5A molecular sieve the effect is very strong (see Figure 5). The lower the temperature, the more polar the column behaves, resulting in much higher retention for carbon monoxide.

For liquid stationary phases, reduced temperature results in a reduced "polar" nature. For such phases it would be desirable to use thicker films to enhance retention and run columns at a higher temperature to make best use of the higher polarity. The challenge is that polar phases also suffer from decreased temperatures stability. Fortunately, the use of silphenylene and trifluoropropyl type building blocks allows phases to exceed 340 °C with an acceptable base line.

Figure 6 shows an example of temperature impact using a phase that was developed for optimal selectivity in the separation of chlorinated pesticides under certain conditions. By changing the oven or flow conditions, different selectivity effects were observed; when faster temperature programming was used at constant flow, pesticides eluted at higher temperatures. The same effects can be obtained when the flow is changed using a fixed temperature program. This selectivity effect usually increases with the polarity of the stationary phase, so it is always important (and interesting) to run a separation at different temperature programs, to learn how and which peaks "move".

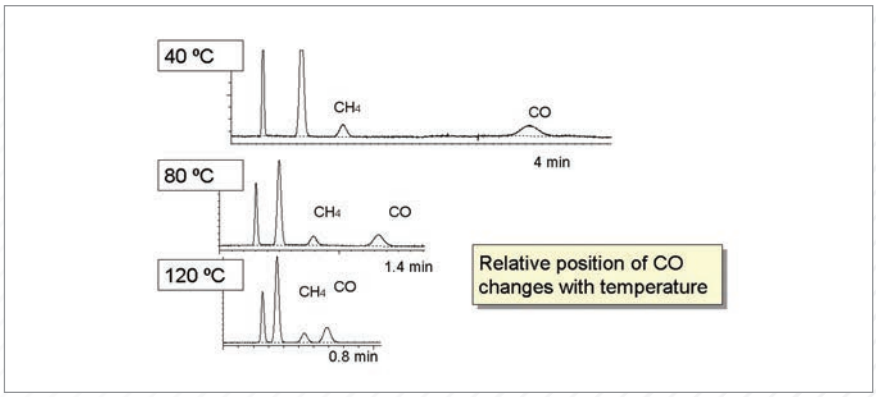

Fig 5. Impact of temperature on Molsieve 5A separation: column behaves in a less polar fashion with higher temperatures, resulting in relative faster elution of CO.

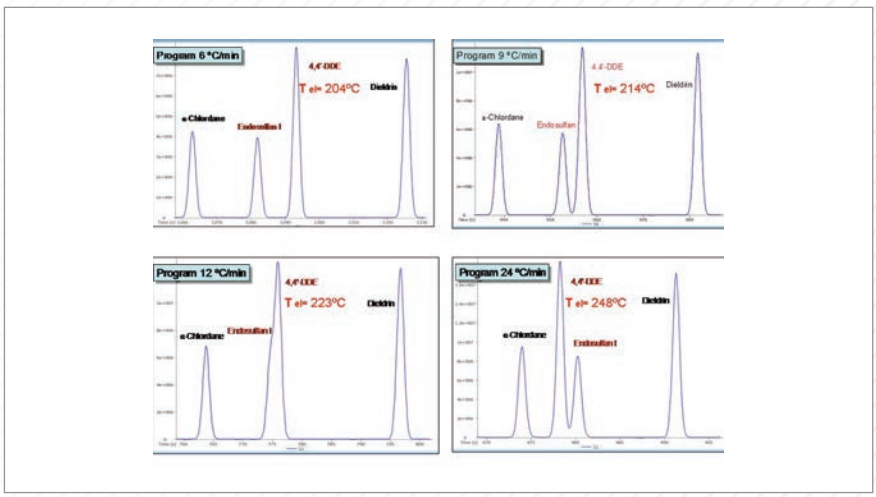

Fig 6. Impact of temperature on pesticide separation using an optimized liquid phase: Rt Cl-Pesticides. With increasing elution temperature, DDE moves relative to endosulfan I and at 24 °C/min these peaks are reversed.

Be smart: get selective

Smart use of stationary phase selectivity allows users to achieve the most efficient separations in the shortest possible time. As such, it should be the first port of call in challenging separations, well ahead of considering column dimensions and operational conditions. In practice, and especially in method development, one has to think about the structures of the compounds of interest and relate that information to the stationary phases available. This is valid for both GC and LC separations (6). The leading commercial companies offer a selection of GC phases that have already been optimized for a certain applications – such phases can be easily recognized as the name is often linked with the application. If there are no application-specific phases, one can use online chromatogram databases and there are even specific programs that can "model" separations.

Jaap de Zeeuw is an international GC specialist at Restek Corporation, Bellefonte, Pennsylvania, USA.

Acknowledgements

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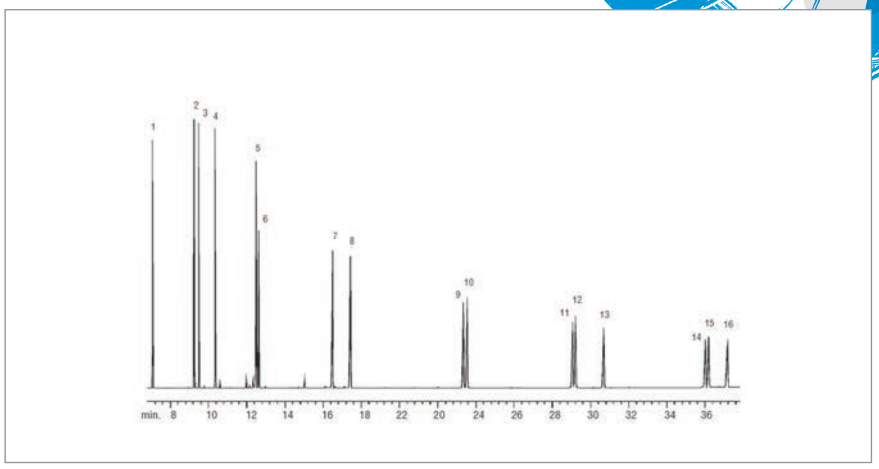

Fig 7. EPA 610 PAH separations on non-polar phase. Column: Rtx-5Sil MS, 30m x 0.25mm, df = 0.5µm; Oven: 40 °C (1 min) > 20 °C/min to 200 °C > 4 °C/min to 310 °C (5 min).

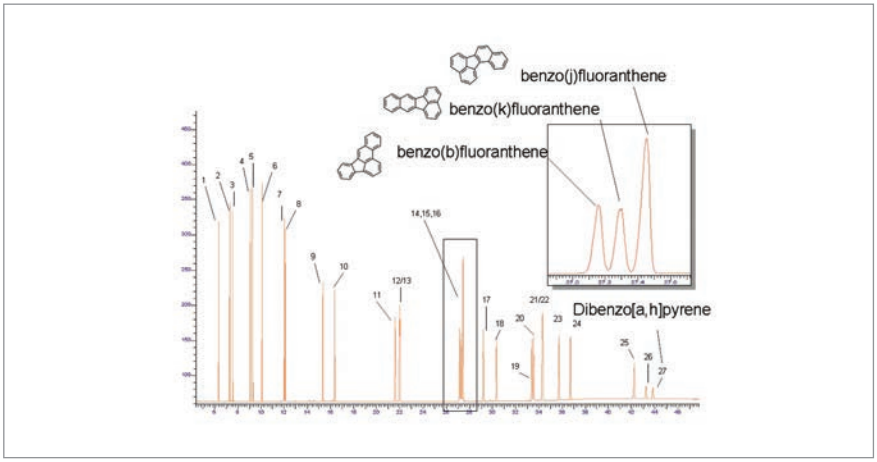

Fig 8. Separations of isobaric fluoranthenes on Rxi-17Sil MS. Full details: bit.ly/15y7k9h

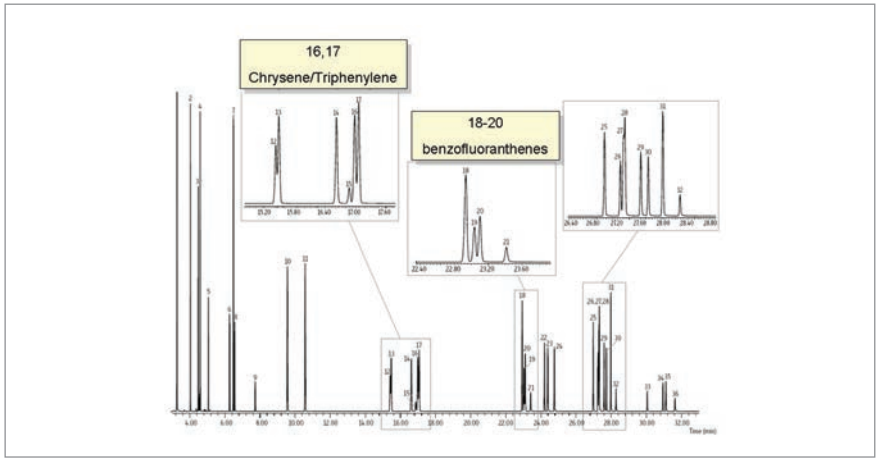

Fig 9. Separation of 35 PAH on new Rxi-PAH phase. Full details: bit.ly/12ohMzu

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Business

Economic drivers
Emerging trends
Business strategies

Triaging Technology – Together

To meet the biopharmaceutical industry's need for improved analytical solutions, Malvern has developed a new approach. Promising technologies derived from a range of sources are rapidly evaluated in close collaboration with biopharma companies, with the best being selected for fast-track development.

By E. Neil Lewis

The breakneck pace of change in the biopharmaceutical sector is challenging many of the established ways that the analytical instruments industry does business. For bold and creative companies and organizations, this opens up exciting new opportunities for collaboration. As an example of this, at Malvern we've taken a radical approach by establishing in 2012 the Bioscience Development Initiative (BDI), an incorporated company within the existing organization. BDI is both independent of Malvern and synergistic with it, and is the vehicle through which we aim to identify and target emerging technologies and be fleet of foot in developing them.

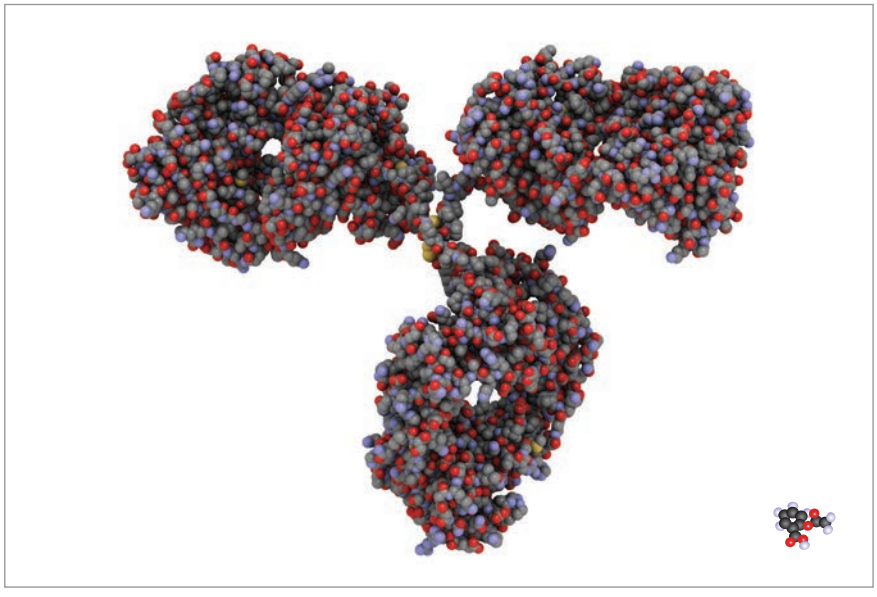

Fig 1. The relative size and complexity of biologic and small molecule drug.

Why be different?

While there is still significant investment in the development of small molecule pharmaceuticals, the seismic shift in enthusiasm and financial focus that is driving the industry in the direction of biologics is inescapable. Biological therapeutics have already moved beyond 'basic' monoclonal antibodies to increasingly sophisticated antibody-drug conjugates, bispecific antibodies, antibody fragments, peptides, and liposomes for targeted delivery, illustrating the huge potential of the sector.

Those working at the leading edge of biopharmaceutical research need analytical tools that will help solve this week's problem, not last month's or last year's. Anticipating the 'known unknowns' and more especially the 'unknown unknowns' of biopharmaceutical research is testing the ingenuity of all concerned. Plus, the rapidly evolving analytical and regulatory requirements add additional complexity, a good example being the opening of the market to biosimilars, the

generic equivalent of biopharmaceuticals.

Figure 1, which illustrates the difference in size between a protein and a small drug molecule, captures the reality of biological pharmaceuticals: protein therapies are very different. They're not the solid dosage forms that the pharmaceutical industry knows so well. They're not powders. They're not tablets. They're delivered intravenously in solution. They're grown, not synthesised or crystallized. The analytical technology to address questions of quality assurance and quality control, and to generate essential data for the pre-formulation and formulation phases of these novel products, is very different from that which the pharmaceutical industry has historically deployed.

Another key driver is cost. While small molecules can be produced at a dollar a gram, providing plenty of material to test, the production of bio-therapeutics costs orders of magnitude more and the quantities available for analysis at the development stage are orders of magnitude less.

A lot of analytical bottlenecks are only now being recognized by the industry, such as the determination of protein aggregation which can affect quality, efficacy and safety. Nanoparticle analysis is also an important consideration that didn't exist a decade ago: some 150 recent new drug applications contain the word 'nanomaterials'.

Understanding what can be measured and what will provide meaningful predictive information on quality, as well as anticipating what measurements will be needed in the future, are massive challenges. That is why Malvern's BDI has been established. We are partnering with major biopharma industry players, encouraging them to share their challenges, and with the leaders in technology development, be they part of established organizations, working in small companies or in academia. BDI's ability to engage both sides of the market is critical to the development of optimal solutions.

Malvern's roots are in particle characterization technology. Over the last decade, our portfolio, capabilities and expertise expanded into materials, biomaterials and biophysical characterization, with a focus on the pharmaceutical industry. We have 40 years' experience in developing, manufacturing and marketing analytical instrumentation, and some of the industry's most talented scientists and engineers. The swing towards biopharmaceuticals set us a new challenge: What would be the best way to harness this capital? How should we develop an entrepreneurial approach that utilizes our expertise and experience to greatest effect in this new and highly dynamic market environment?

Finding the solution

The Malvern BDI is incorporated in the USA, operating from a facility in Columbia, Maryland. It is decentralised, a separate development group focussed on intellectual property and addressing the sea change in the pharmaceutical industry.

We don't believe that Malvern will come up with all of the good ideas for instrumentation, so we have a broad remit that considers three sources. One is technology acquisition: we go out and assess ideas from many different places. Another is through licensing agreements, which could be with small companies or universities. And some products will, of course, come about through organic development within the company. These three pipeline sources will come together to shape Malvern's long-term strategy for this market.

Once we have the product leads, we are working on shorter, tighter, customer-facing development cycles. We recognize that it's not just industry R&D that is changing, the regulatory environment is evolving too. Biopharmaceutical companies have to keep pace, whether for biosimilars or simply in relation to the efficacy and safety of biological products.

How BDI works

The structure of our workflow is illustrated in figure 2. It places BDI at the center; this includes people such as project managers and high level scientists. To the left sit universities, intellectual property (IP) and small technology start-ups. We in BDI are constantly assessing the opportunities that these sources present and we can invest in promising technologies to bring them to market more quickly. However, the really unique aspect of the approach is that we take some of these embryonic ideas – ones that may not be quite ready for 'prime time' as fully fledged products but are far too interesting to ignore – and push them straight into biopharmaceutical companies. What we are looking for from biopharma is quick, iterative learning.

In the dialogue and testing process it may become apparent there is a compelling technology or product. Most developers don't have the resources to quickly embed into an environment like biopharmaceuticals so we can move development over to Malvern Limited, into the regular engineering and product management team – the right hand part of the picture.

This is a quite different approach from traditional analytical instrument development, which generally involves generating a requirement specification, producing a prototype, testing it against the requirement specification and continuing along a well-trodden pathway through to launch. Within BDI we're talking to biopharma customers early and bringing them right into the development loop, pushing the prototype

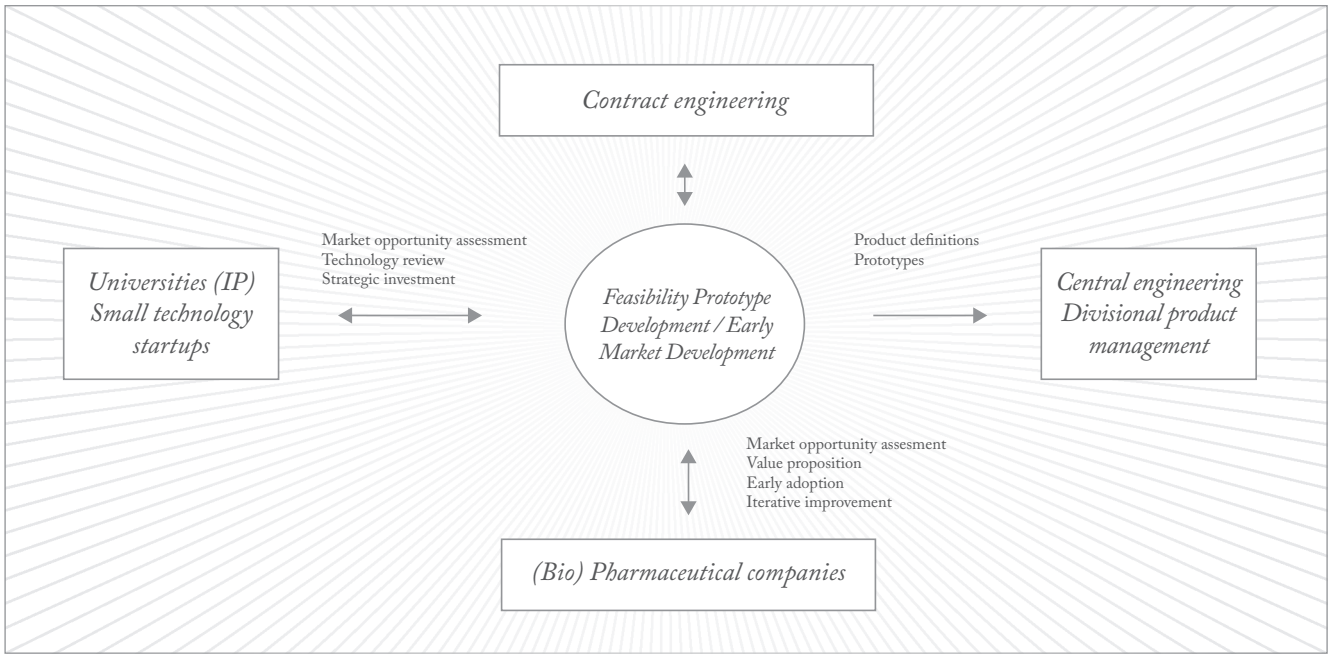

Fig 2: The BDI workflow

back to them. The reaction from most of the major biopharmaceutical companies we've talked to has been overwhelmingly positive. They want to be part of the development process and welcome being able to help direct it. Essentially we're providing a relatively low-risk opportunity for them to test out novel ideas, in some cases to immediately apply them and steal a march on the competition, and to provide feedback that helps determine the next step.

The idea is really resonating in an industry that acknowledges 'we don't know what we don't know'. Through BDI, Malvern can bring technologies to the table that perhaps no-one has heard about, show a prototype, run some samples, or bring it into the biopharma facility. Then we look at the data together and determine whether or not this technology or product has some utility. If it's not going to solve any problems, we cut if off at the pass. While no-one likes to fail, the mentality within BDI is 'fail fast, fail cheap'. In a market so fluid that you can't guarantee it's going to be the same in six or twelve months, let alone two or three years, who wants to be responsible for developing the answer to a redundant question?

It's pretty clear that to bet right now on a single technology in the biopharma market would be risky, so we're spreading the bet across a number of different technologies. Through interaction with customers we will determine the likely winners, triaging as we go. This can only work through high-level partnering, with 'the customer', who at some point we hope will become a real paying customer. For now, it's amazing the number of people I've talked to who have said, "We really like that idea. It allows us to spread our options and really figure out what's helpful for us."

The first products from BDI are already coming through. They include an agreement with Affinity Biosensors to employ their Resonant Mass Measurement technology to detect and count particles in the size range 50 nm - 5 μm, especially useful for characterizing protein aggregates in a formulation or buffer, and the results of a partnership and development program with a small company to develop microviscosity measurement technology, which will be marketed as a full Malvern product later in 2013.

We are continually seeking out technologies, adding them to our toolbox and trying to evaluate them as quickly as we can in terms of market suitability. We know things are changing. The customer knows they're changing. The FDA knows they're changing. There is no room for any of us to be sluggish. BDI is a capacitor, or an interface, with the ability to embrace and assess the changes and seamlessly slide new technologies into the mainstream portfolio.

E. Neil Lewis is Chief Technology Officer, Malvern Instruments and President of Malvern Biosciences, Inc.

Solutions

Real analytical problems
Collaborative expertise
Novel applications

Sound Dilutions

Acoustic liquid handling prevents a pernicious error that is wasting time, costing money and generating misleading results in drug development.

By Joe Olechno, Sean Ekins, and Antony J. Williams

The Problem

Significant systemic errors in high-throughput screening of compounds (HTS) are generated by the use of pipettes and serial dilution processes. These errors, which include high rates of both false positive and false negative results, can mislead researchers on which compounds will make the best drug candidates and misdirect the development of subsequent compounds. The problem is widespread and deeply entrenched.

Background

HTS is extensively used by all major pharmaceutical companies in their quest to discover new drugs. The estimated global market for HTS in 2017 is estimated to be $19.9 billion annually (1). The tremendous growth in screening of millions of compounds has been driven by a number of simultaneous advancements in science including parallel organic synthesis (which generates more compounds) and improvements in genomics and proteomics (which identify druggable targets that can be used in HTS).

Pharmaceutical scientists constantly search for compounds that will bind to specific targets (receptors and enzymes), usually with the purpose of turning off the activity of the target. Inhibitors that bind tightly are excellent candidates for new drugs. Activity or potency is usually measured by analyzing an enzyme in the presence of varying concentrations of an inhibitor and determining at what level there is a 50 percent inhibition of activity (the IC50 value). The lower the IC50 value, the stronger the inhibitor and the better the drug candidate.

The traditional mechanism to generate a range of concentrations is serial dilution: a fixed volume of a concentrated solution is diluted with a fixed volume of fluid. After mixing, a fixed volume of this newly generated solution is transferred to another vessel and diluted again. This step-wise process may be repeated multiple times to generate all the different required concentrations of the inhibitor to enable the generation of an IC50 experiment.

The three-dimensional structures of the small molecule inhibitors and their associated IC50 values can be used to generate a model of the binding site of the target protein (a pharmacophore). The ability to generate a good pharmacophore is of immense help to the researcher. It suggests the presence or absence of features necessary in the small molecule for interactions with the protein, be they hydrogen bond donors, hydrogen bond acceptors, hydrophobic regions, etc., and their relative locations. An accurate pharmacophore allows researchers to predict the level of inhibition of potential new compounds from the structures of small molecules alone.

The Solution

An alternative liquid handling process is acoustic liquid handling, as embodied by the Labcyte Echo liquid handler, produced by the company for which one of the authors (JO) works. As illustrated in Figure 1, it uses focused sound energy to eject upward a small but very precise droplet of fluid, thereby eliminating the use of any pipettes, nozzles or physical contact. Droplets are captured by an inverted container. Since surface tension is stronger than the force of gravity, the liquid does not drop back down. The ability to transfer liquids on a drop by drop basis (down to 2.5 nanoliters) can generate dilutions directly by varying the amount of concentrated inhibitor, rather than by using serial dilution techniques (2-4). Further, there is no potential for cross-contamination of the solutions due to dirty tips or from carry-over. Nor is there a possibility for the introduction of plasticizers and other components (leachates) from the plastic surfaces or tips into assays. It also reduces use of organic solvent in the final assay.

In a recently published paper (5), we looked more closely at the impact of the type of liquid handling on IC50 values and the pharmacophores generated from those values. Researchers at AstraZeneca disclosed data in a US patent and in an international patent application (6,7) for potential cancer therapeutics. It showed radically different IC50 values depending on the dispensing technique and the use of direct versus serial dilution. Acoustic dispensing suggested that all the synthesized compounds listed were highly active inhibitors. The same compounds tested with traditional liquid handling and serial dilution generated poor IC50 values and, likely, would have been passed over for further study. We sought to understand the implications of the AstraZeneca results that showed as much as a 276-fold difference in IC50 values.

We used the AstraZeneca data to create two separate pharmacophores, one based only on the pipetting data and the other on the acoustic data. As expected from the dramatically different IC50 values, the two pharmacophores were very different. But which was the better model?

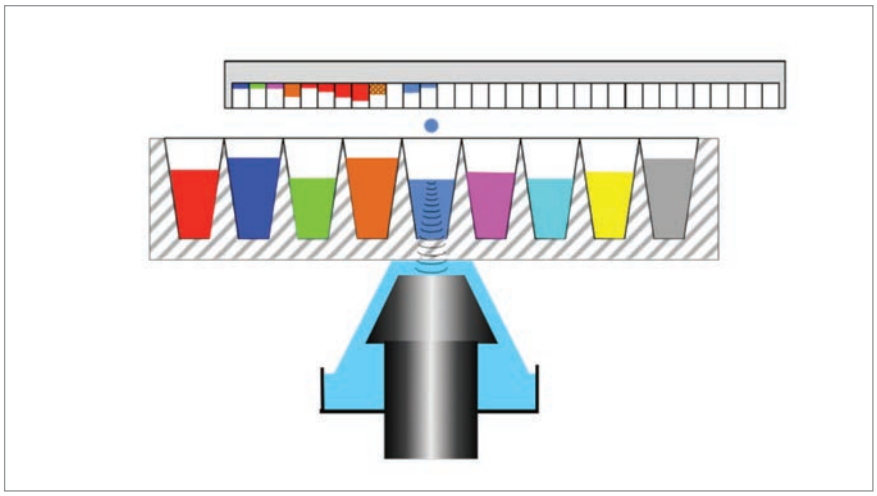

Fig 1: Acoustic energy is transmitted by a transducer through the bottom of a multi-welled reservoir and focused at the fluid meniscus. This causes a volumetrically precise droplet of fluid to be ejected from the source plate. The droplet is captured at the destination by surface tension. To transfer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

We tested the two pharmacophores for their predictive capabilities on a new set of compounds (8). The results were dramatic. The pipette-based pharmacophore was non-predictive: measured IC50 values were at odds with the predicted values and it did not correctly order the inhibitors from most to least potent. The acoustic-based pharmacophore did correctly order the new inhibitors in the rank obtained experimentally. Had the AstraZeneca researchers been limited to the pipette-based results they would likely have generated the next set of compounds based on a non-predictive model. This would have taken them in a different direction, wasted resources and failed in the discovery of a new family of drugs.

We subsequently discovered X-ray crystallographic studies from AstraZeneca that strongly supported our initial results. Four papers (9-12) were published that provided X-ray crystallographic data for the receptor in question with inhibitors in the binding site. We also generated pharmacophores based on the X-ray structure information. Table 1 compares the binding features of the pipette-based pharmacophore, the acoustics-based pharmacophore and the average of the ten crystal-based pharmacophores. All the X-ray crystallographic pharmacophores indicated the presence of hydrophobic binding as did the acoustics-based pharmacophore. The pipette-based pharmacophore was noticeably missing such a region. Not only is the acoustics-based pharmacophore more predictive but it more closely resembles the true enzyme binding site feature requirements.

Beyond the Solution

For this particular receptor and with these specific compounds, the acoustic technology coupled with direct dilution generated much better results. The

Table 1. Numbers of different features in pipette-based, acoustics-based and crystal-based pharmacophores.

Pharmacophore	*Hydrophobic features*	*Hydrogen bond acceptors*	*Hydrogen bond donors*
Pipette-based	0	2	1
Acoustic-based	2	1	1
Crystal-based (average of 8)	2.5	1.4	0.9

acoustic-based pharmacophore was predictive and closely resembled the pharmacophores developed by X-ray crystallography. But the cautious researcher might still be hesitant. After all, serial dilutions have been used for decades. Is this a particularly strange circumstance?

Results reported by pharmaceutical companies over the last decade suggest that this problem is widespread (13-15). Over 10,000 compounds have been tested with high rates of false positive and negative results for traditional liquid handling. There is a strong bias for pipette-based techniques to suggest compounds are less active than they are when transferred with acoustics using direct dilution. This suggests that hundreds of very useful compounds are being incorrectly ignored because they do not seem potent enough to carry forward. Even more worrisome is that the skewed data from pipette-based serial dilutions will contaminate the company databases and lead to structure-activity relationships that mislead researchers into the costly synthesis and testing of compounds that are bound to fail.

We encourage the pharmaceutical industry, academia (where HTS is rapidly increasing) and others such as the NIH to continue to confirm or disprove our findings. We know that several companies have made comparisons of direct dilution via acoustic liquid handling with serial dilution via traditional liquid handlers and are seeing similar data as evidenced by posters and presentations at meetings, but more data would be helpful. We also strongly encourage the use of metadata in databases to include the type of dilution method and liquid handling used. Based on our data, it is clear that IC50 results can vary drastically between the two techniques. Aggregating the results together would seem to be a recipe for disaster, resulting in a loss of precision and accuracy as well as predictive power.

Are your assays providing information that leads to the development of new drugs or does it take you down a cul-de-sac? While we do not wish to oversell the impact of the failure of serial dilutions, this case suggests that there may be other instances in which pharmaceutical and academic researchers followed dead-end compounds in a doomed attempt to discover new drugs. In light of well-publicized failures of HTS to fulfill possibly exaggerated utility, we wonder how much of the problem may lie with liquid handling procedures, which is ultimately a problem that can be readily rectified.

Joe Olechno is Senior Research Fellow at Labcyte Inc., Sunnyvale, California, USA; Sean Ekins is Senior Consultant, Collaborations in Chemistry, Fuquay Varina, North Carolina, USA, and Antony Williams is VP of Strategic Development for the Royal Society of Chemistry, Wake Forest, North Carolina, USA.

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Introducing the latest in UHPLC technology

Peptide mapping method uses a novel high resolution column with new UHPLC technology.

Peptide Mapping uses UHPLC to check the constituent amino acids by comparing the pattern of the peptide fragment chromatogram after the enzyme digestion of protein. Recently, this method has also been applied to quality control testing of bio-pharmaceutical therapies.

As a result, it is important that the chromatography is of high resolution and high speed with very low variability. Here, the high resolution, high speed measurement result using the ChromasterUltraRs is introduced. BSA digest was used as model sample, and a comparison was made between conventional and high resolution columns. The peak capacity (4σ) for each column was then compared.

Such a Peptide Mapping method is specified as a test method following the harmonization of three pharmacopoeias, namely JP, EP and USP.

It was calculated from the results that the new high resolution, high speed analysis with the LaChromUltra II column and ChromasterUltraRs UHPLC system gives 1.4 times better peak capacity and half the analysis time compared to the chromatogram using a column with 5 µm particle size.

The ChromasterUltraRs

The ChromasterUltraRs is an excellent tool for peptide mapping applications owing to its highly stable pump technology, very low carry over autosampler and ultra-sensitive detector flow cell.

Drawing on 30 years of engineering highly robust and durable HPLC systems, the ChromasterUltraRs is based on the renowned high quality engineering of Hitachi with many new innovations that improve reliability of results, laboratory work flow and method transfer.

To book a demonstration of this outstanding new system, please email us at chromatography@eu.vwr.com or contact your local VWR representative.
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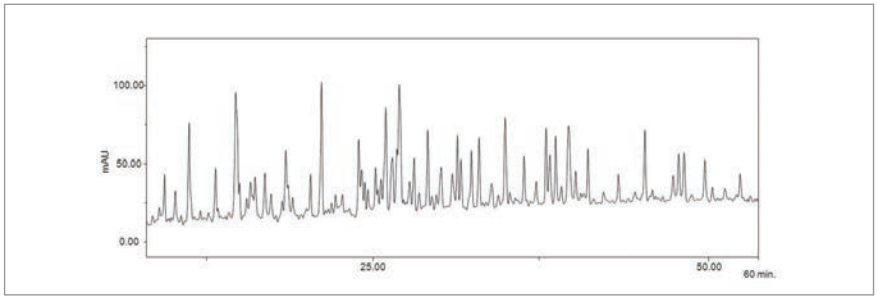
ChromasterUltraRs

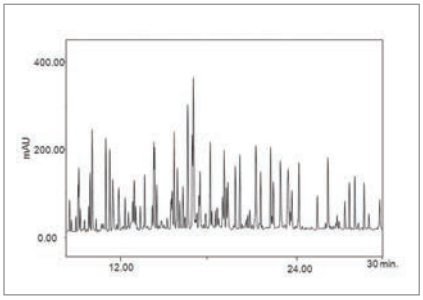
Column	LaChromUltra II C18 4.6×250 mm, 5 µm
Column temperature	40 °C
Flow rate	1.0 ml/min
Eluent	(A) 0.1%-TFA/H20 (B) 0.1%-TFA/CH3CN
Gradient	5% B (0 min.) → 45% B (60 min.)
Injection volume	10 µl (about 100 µg)
Detection	215 nm
Max. pressure	12 MPa (120 bar)

Chromatogram of BSA digest obtained using the ChromasterUltraRs and a LaChromUltra II C18 column of dimensions 4.6×250 mm with a particle size of 5 µm (Peak capacity 4σ =264)



Column	LaChromUltra II C18 3.0×250 mm, 1.9 µm
Column temperature	40 °C
Flow rate	0.85 ml/min
Eluent	(A) 0.1%-TFA/H20 (B) 0.1%-TFA/CH3CN
Gradient	5% B (0 min.) → 45% B (30 min.)
Injection volume	5 µl (about 50 µg)
Detection	215 nm
Max. pressure	135 MPa (1350 bar)

Chromatogram of BSA digest obtained using the ChromasterUltraRs and a LaChromUltra II C18 column of dimensions 3.0×250 mm with a particle size of 1.9 µm (Peak capacity 4σ =368)



Detailed hydrocarbon analysis (DHA) using ASTM method D6729 and D6729 appendix X2.

Authors: Ed Connor, Dr.Sc, Peak Scientific, Glasgow UK & Joaquin Lubkowitz, PhD, Separation Systems, Florida, USA.

Detailed hydrocarbon analysis (DHA) is a separation technique used by a variety of laboratories involved in the petrochemical industry for analysis and identification of individual components as well as for bulk hydrocarbon characterisation of a particular sample. Bulk analysis looks at gasoline composition in terms of PONA components (Paraffins, Olefins, Naphthalenes and Aromatics) and other fuels in the C1-C13 range since this gives an indication of overall quality of the sample.

The analysis of gasoline for spark ignition components is essential for quality control. Owing to the complex nature of gasoline samples, good resolution between eluents is required and therefore a long column is used (typically 100m). Several methods are routinely used for DHA which differ in their oven temperature ramp rates or in the length of column used. Each method has its advantages and disadvantages since some improve peak resolution of low boiling compounds whereas others provide better resolution of heavier compounds at the end of the chromatogram. The complex nature of the methodology coupled with the use of such a long column means that run times can easily exceed 120 minutes when using helium carrier gas. However, the use of hydrogen can vastly increase run rates because of its efficiency at higher linear velocities. This is a particularly attractive prospect for oil analysis laboratories since faster throughput of sample means increased profitability. The benefits of using hydrogen in terms of improved chromatography combined with the increasing cost of helium along with supply issues means that laboratories switching from helium to hydrogen can become much more profitable whilst maintaining standards of analysis that conform to industry standards.

This application note demonstrates a comparison of gasoline analysis using helium carrier gas following ASTM method D67291 and the use of unfiltered hydrogen carrier gas produced by a Peak Scientific Precision Trace hydrogen generator in DHA following ASTM method D6729-1 appendix X2 and demonstrates the improvement in run time whilst maintaining crucial separations between certain components.

Results and discussion

Detailed hydrocarbon analysis of gasoline showed that the elution time of the last compound in the mixture, n-Pentadecane, could be reduced from 125 minutes to less than 74 minutes by switching carrier gas from helium to hydrogen (Figure 1). Despite the difference in analysis times, the PONA analysis showed that quantitative differences were not significantly different when using either carrier gas (Table 1). Despite the much higher carrier gas flow rates when using hydrogen carrier gas, critical separations were still achieved in most cases and in certain cases were even improved. Separation of 1-methylcyclopentene and benzene, which is highly regulated analysis because of the importance of the benzene fraction, was actually improved when using hydrogen carrier gas despite the quicker elution times of the compounds with hydrogen as a carrier gas (Figure 2). Separation of Toluene and 2,3,3-Trimethylpentane was achieved using helium whereas with hydrogen the two compounds co-eluted (Figure 3). To separate these two compounds using hydrogen carrier gas some improvements to the method would need to be made. Separation of Tridecane and 1-methylnaphthalene was achieved equally well using both carrier gases (Figure 4).

The results of the DHA show that the use of hydrogen as a carrier gas, following ASTM D6729 appendix X2 methodology can vastly reduce analysis times for gasoline analysis whilst providing the necessary resolution required for separations of critical components.

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2. *Designation D6729 – 01 Appendix X2. Hydrocarbon data using hydrogen carrier. ASTM International 2004.*

Carrier gas	Hydrogen	Helium
Carrier gas source	Peak Scientific Precision 500 hydrogen generator	Cylinder helium from Airgas (99.999%).
Eluent	Gasoline	Gasoline
Injector Temperature	280	280
Injection volume	0.2	0.2
Split ratio	250:1	250:1
Column	100% dimethylpolysoloxane, 100 m, 0.25 mm, 0.5 µm film thickness (J&W)	100% dimethylpolysoloxane, 100 m, 0.25 mm, 0.5 µm film thickness (J&W)
Column flow	2.5 mL/min	1.8 mL/min
Oven Initial Temperature	35 °C (7.70 min hold)	35 °C (13 min hold)
Oven ramp 1	17 °C/min to 45 °C (8.80 min hold)	10 °C/min to 45 °C (15 min hold)
Oven ramp 2	1.7 °C/min to 60 °C (8.80 min hold)	1 °C/min to 60 °C (15 min hold)
Oven ramp 3	3.39 °C/min to 220 °C (2.92 min hold)	2 °C/min to 220 °C (5 min hold)
Gas chromatograph	Agilent 7890A	Agilent 7890A
Detector	FID	FID
Method	ASTM D6729 Appendix 2	ASTM D6729
Analysis software	Hydrocarbon Expert 5.10 (Separation systems)	Hydrocarbon Expert 5.10 (Separation systems)

Table 1: Designation D 6729-01 Standard Test Method for Determination of Individual Components in Spark Ignition Engine Fuels by 100 Meter Capillary High Resolution Gas Chromatography. ASTM International 2002.

Group	% Weight	% Weight	Difference
Paraffin	10.990	10.749	0.241
I-Paraffins	31.846	31.795	0.051
Aromatics	42.605	42.953	-0.348
Mono-Aromatics	40.211	40.466	-0.255
Naphthalenes	1.090	1.133	-0.043
Indanes	0.731	0.755	-0.024
Indenes	0.573	0.600	-0.027
Naphthenes	4.676	4.926	-0.249
Mono-Naphthenes	4.676	4.926	-0.249
Di/Bicyclo-Naphthenes	0.000	0.000	0.000
Olefins	9.835	9.455	0.381
n-Olefins	3.258	2.947	0.311
Iso-Olefins	5.683	5.676	0.007
Naphtheno-Olefins	0.869	0.784	0.085
Di-Olefins	0.026	0.047	-0.021
Oxygenates	0.000	0.000	0.000
Unidentified	0.047	0.122	-0.075
Plus	0.000	0.000	0.000
Total	**100.000**	**100.000**	

Table 2. Quantitative results of PONA compounds.

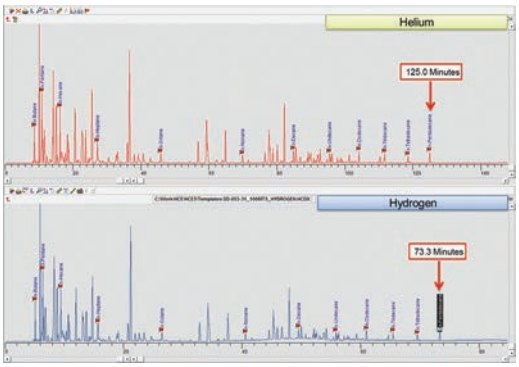

Fig 1. Comparison of DHA of total gasoline sample using hydrogen and helium.

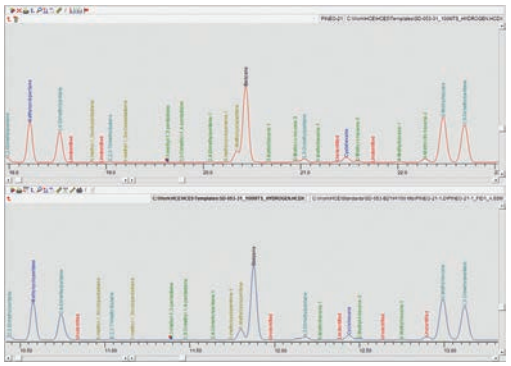

Fig 2. Comparison of separation of 1-methylcyclopentene and benzene when using hydrogen and helium as carrier gas.

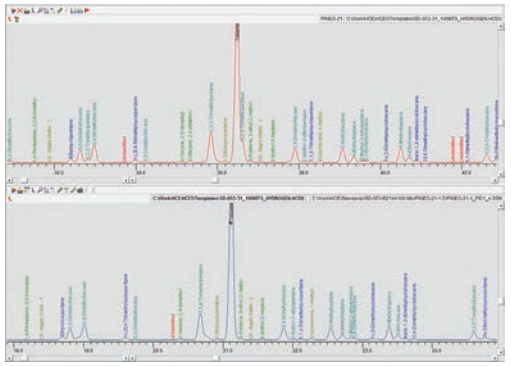

Fig 3. Comparison of separation of Toluene and 2,3,3-Trimethylpentane when using hydrogen and helium as carrier gas.

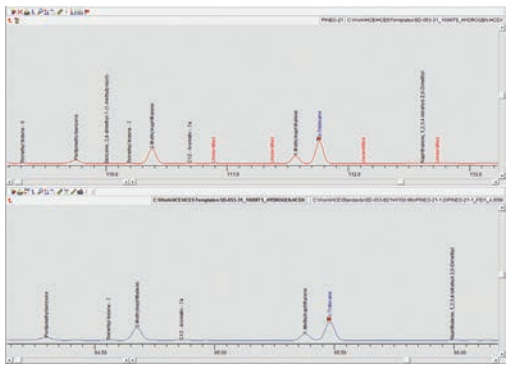

Fig 4. Comparison of separation of Tridecane and 1-methylnaphthalene when using hydrogen and helium as carrier gas.

The Distinguished Scientist

Richard D. Smith, Chief Scientist of the Biological Sciences Division at Pacific Northwest National Laboratory, reflects on 40 years in mass spectrometry following his Distinguished Contribution award at ASMS 2013.

How does it make you feel to be recognized as making a "distinguished contribution to mass spectrometry"?

The field of mass spectrometry (MS) has grown greatly in importance in recent years, particularly for biological applications where MS is the 'go to' tool for many key -omics measurements – proteomics, metabolomics, lipidomics, glycomics. They are what I refer to as 'pan-omics'. I feel honored and humbled to be recognized as contributing to this endeavor, and also recognize that really this award extends to the fantastic set of colleagues, past and present, at PNNL.

How did you find your way into your career?

It goes back to the mid-1970s – very early in my career – when I was thinking about what large research impacts might be enabled by MS. At that time, there was a very small community pursuing the development of MS for what are now considered extremely simple biological applications. Applying MS for the characterization of whole 'biological systems' was really not discussed; the possibilities then were greatly constrained by some really difficult problems: lack of sensitivity, limitations of MS ionization methods, separation methods to which MS could be interfaced, and a range of other MS capabilities. I was intrigued by these problems, and realized that if they could be solved, MS could become an integral technique for biological research.

My career has centered on addressing these MS technology issues and applying the improved techniques in as broad a context as possible. It's fun to be part of a much larger research agenda and contribute to areas that can affect all of us in one way or another, for example, in cancer-related research or improving biofuel production. Importantly, our applied work also provides continuous feedback on which technical issues are limiting – presenting a better focus for our technology development efforts.

"What we really need is to take MS-based proteomics, metabolomics, lipidomics and related measurements, and be able to make them not just ten times faster but a million times faster."

What is the most exciting development in MS technology that you have seen in the last five years?

There have been many, but advances in the sensitivity and resolving power of ion mobility separations in conjunction with MS are at the top of my list. The ability to add a fast stage of separation, and to do this in an essentially lossless fashion is a huge advance. Such advances not only help to better deal with biological complexity, but also provide additional information (for example, protein-shape-related mobility data), and actually also increase the dynamic range of the measurements and the sensitivity achievable. I suspect that ion mobility separations will become an increasingly common component of MS instruments.

You are described as having an "obsession for sensitivity" – what drives this obsession and where is it likely to lead you next?

Actually, I think of myself as having a 'passion for sensitivity', but the difference between passion and obsession is in the eye of the beholder… More seriously, what drives this is the desire to better characterize, and ultimately understand, biological systems. And this gets to what I really want to focus on next. If you look at what we really need to effectively apply systems biology approaches, it will require much, much more data across the pan-omics data types (for example, proteomics). However, the throughput of present measurements (that is to say, the rate at which we can make measurements and fully analyze samples) lags by many orders of magnitude behind what can now be done in genomics. What we really need is to take MS-based proteomics, metabolomics, lipidomics and related measurements, and be able to make them not just ten times faster but a million times faster.

The direction I spend more and more time thinking about involves completely new paradigms in which we can manipulate and separate ions in highly parallel, lossless, and complex ways, and then analyze them in massively parallel MS systems. And while the key pieces are already beginning to coalesce, there are still significant challenges for doing this, not least being how to deal with the enormous flood of data that these new platforms will produce. But staggering advances in computation are continuing and this community is learning quickly from dealing with the advances in genomics, so there are lots of reasons for optimism.

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