FEBRUARY 2017 # 49

the Analytical Scientist

Analytical Science Sans Frontières

It started with an old GC instrument. Ten years on, a thriving cross-border collaboration is giving Africa's analytical community a boost.

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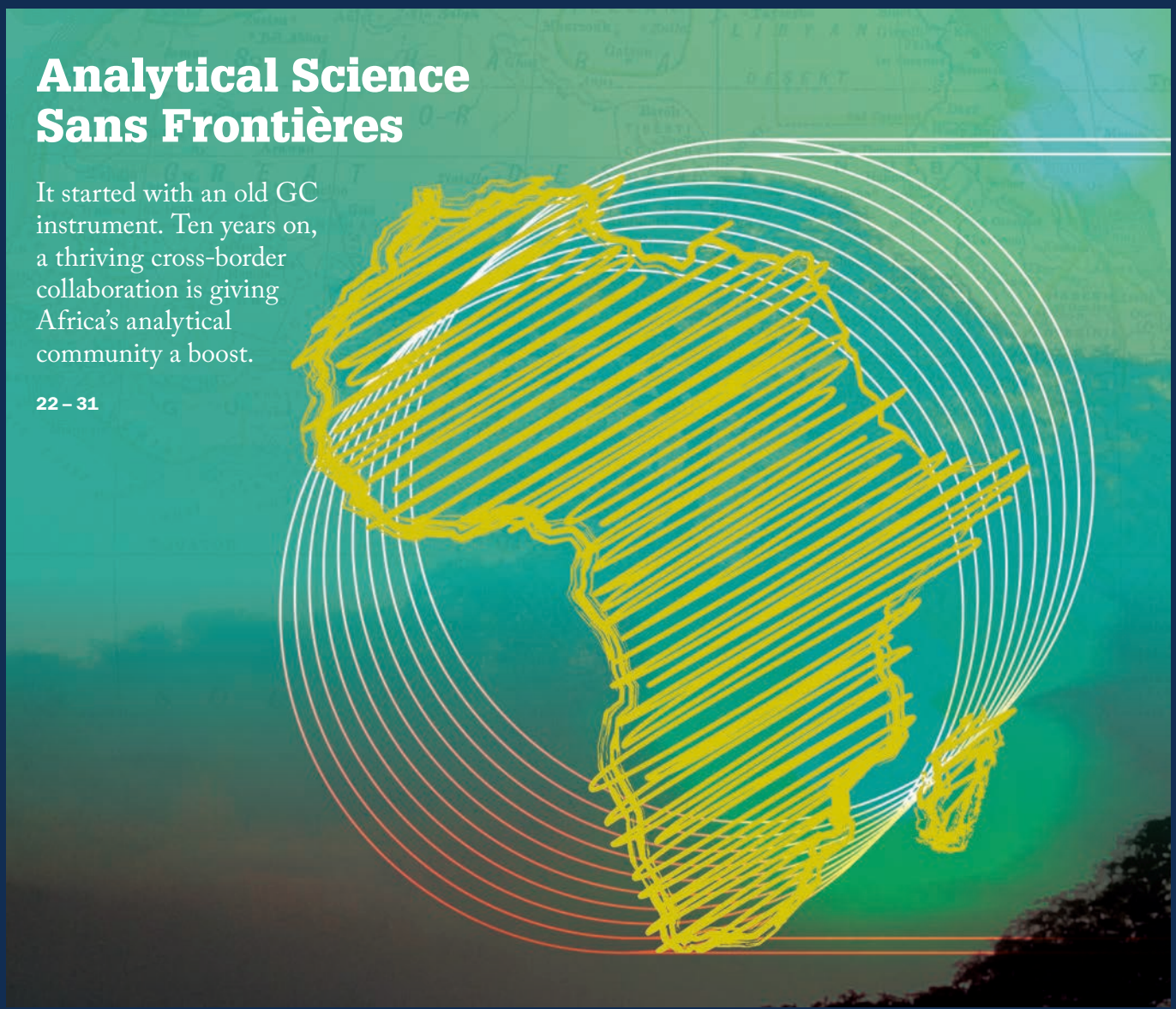

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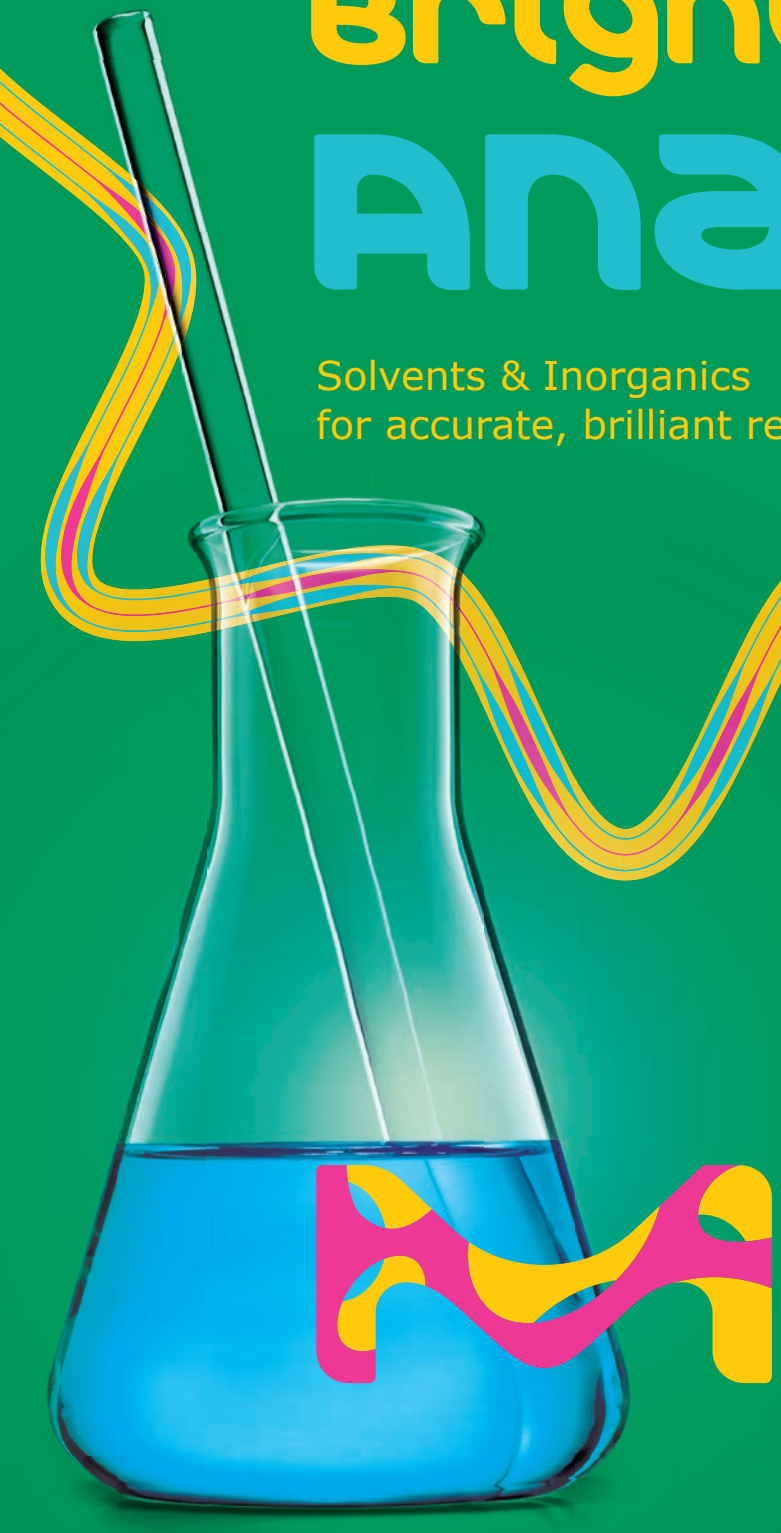

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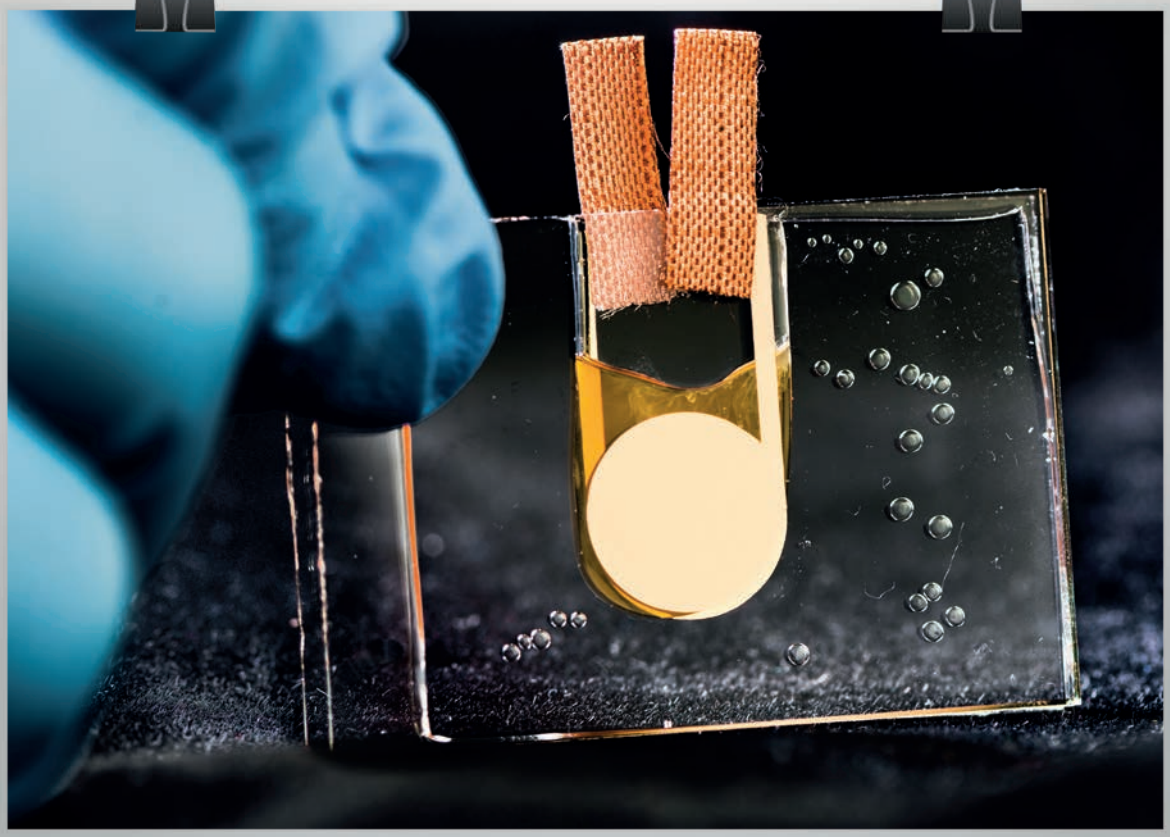

The Heat is On

Meet the world's first heat-controlled transistor, created by a team from the Organic Electronics Laboratory at Linkoping University (1). Combining an ionic thermoelectric supercapacitor (ITESC) and an electrolyte-gated transistor, its sensitivity to heat is estimated to be over 100-times greater than traditional thermoelectric sensors. The inventors believe that the technology has potential as an inexpensive sensor in infrared cameras, and even in functional dressings, as a means to monitor the healing process.

Credit: Thor Balkhed, Linkoping University, Sweden.

Reference: 1. D Zhao et al., "Ionic thermoelectric gating organic transistors", Nat Commun, 8 (2017).

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Celebrating Africa's analytical community.

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the Analytical Scientist

ISSUE 49 - FEBRUARY 2017

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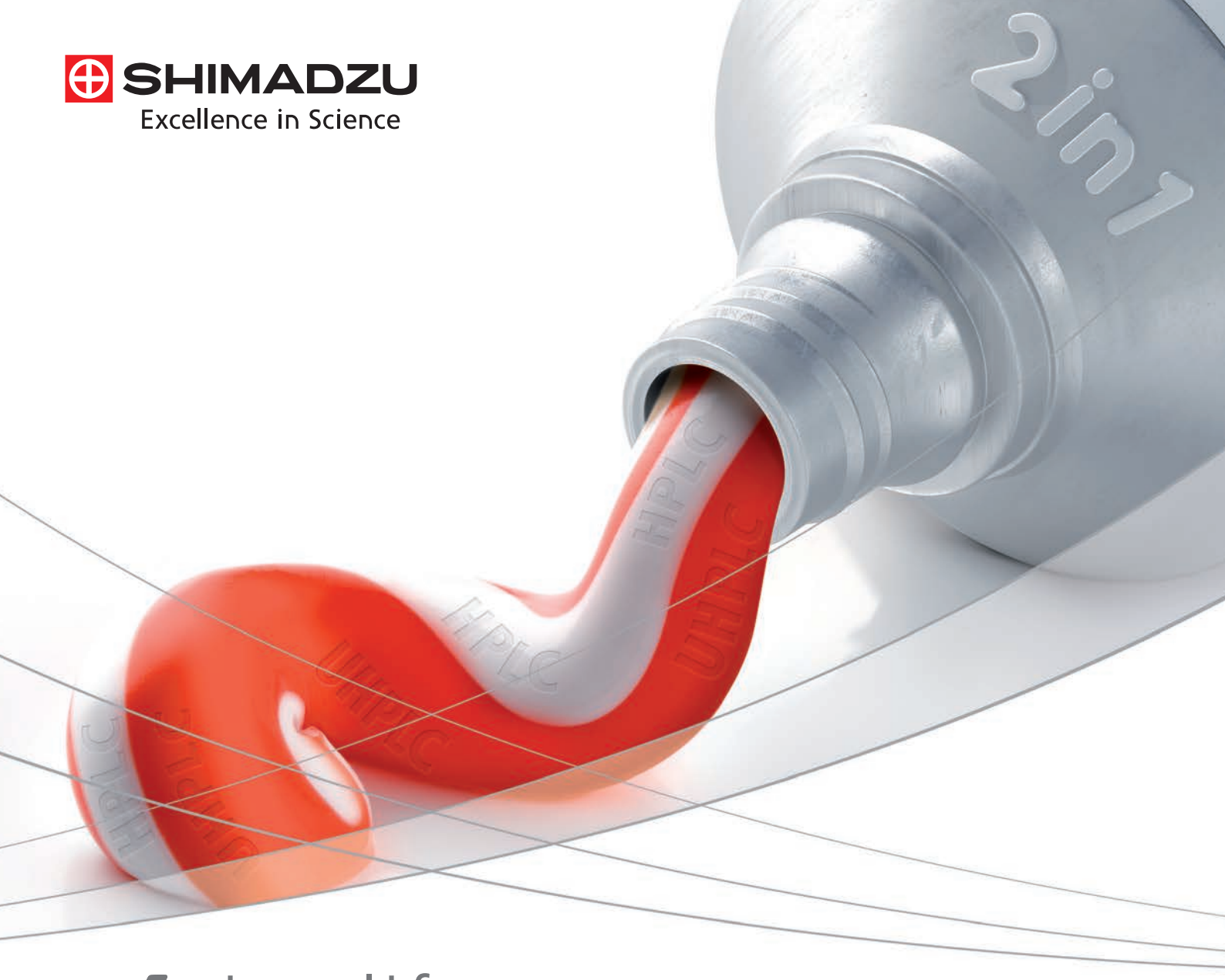

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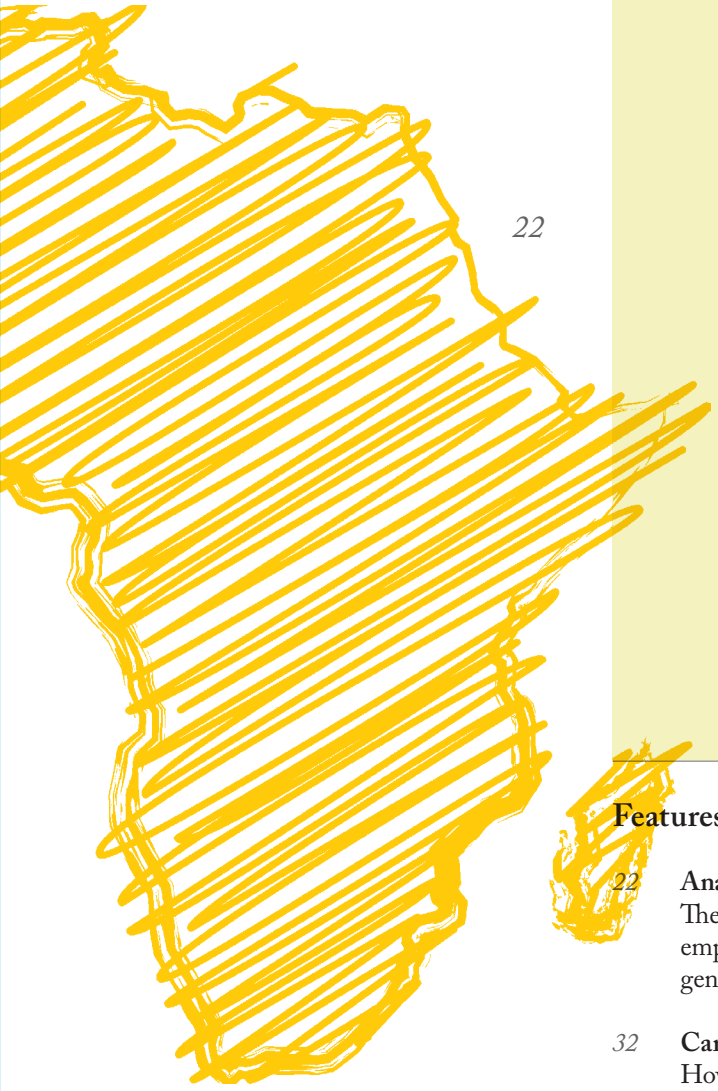

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Addressing a State of Disunion

The US travel ban strikes at the collaborative heart of science

The prevailing theme of this issue is collaboration – from the growing analytical community of Africa (page 22), to Spanish and Finnish researchers teaming up to turn back time (page 12), to innovative academic–industry partnerships (page 42). In fact, collaboration could be mooted as a key theme of almost any issue of The Analytical Scientist, and indeed our sister titles in ophthalmology, drug manufacture, pathology and translational science. A few scientists may find teamwork challenging (see John Griffiths's toe-curling stories of authorship acrimony on page 17), but most would agree that collaboration and exchange of ideas is the lifeblood of science.

So it's not surprising that news of President Trump's 'travel ban' – an executive order restricting travel to the US of citizens from seven Muslim-majority countries – was greeted with dismay by many in the international scientific community (1–6).

US universities, pharma companies, engineering firms and non-profits are a melting pot of nationalities. Now, thousands of scientists and engineers may find themselves unable to attend conferences or visit loved ones overseas for fear of being deported on their return. Labs are unable to welcome students, new employees or collaborators from the seven countries, nor meet them at the many international conferences held each year in the US.

Though the executive order has now been blocked by the US courts, Trump remains determined to see the ban reinstated.

Over 42,000 academics have signed a petition against the ban, including 62 Nobel Laureates (1). Some 180 US STEM organizations issued a joint letter condemning the executive order, and laying out the myriad ways it would harm science in America (2). The letter states: "Scientific progress depends on openness, transparency, and the free flow of ideas and people, and these principles have helped the United States attract and richly benefit from international scientific talent."

As a supporting science, analytical chemistry is, by its very nature, collaborative. On page 51, Milton Lee says, "That's how you get creativity – by building up ideas together" – and anything that disrupts the free flow of ideas can only be bad for science.

What's your view on the ban? Have you or your colleagues been affected? Get in touch at charlotte.barker@texerepublishing.com.

Charlotte Barker
Editor

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4. *Science Undivided. http://bit.ly/2l8kbxT*
5. *Freedom of Science Network. http://bit.ly/2kkUMgF*
6. *March for Science. http://bit.ly/2l0Vbp3*

Upfront

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

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

Measuring Your Brain Activity on Google Glass

Neuroergonomics, smartwear, spectroscopic brain imaging... Analytical science has never felt so futuristic

Neuroergonomics was defined by the late Raja Parasuraman as "the study of the human brain in relation to performance at work and in everyday settings" (1). But working against his vision is the fact that brain imaging studies tend to be restricted to artificial settings and simulations of actual tasks because of data collection limitations (for example, being tied to a large MRI machines). So when Hasan Ayaz (Drexel University) presented Raja Parasuraman and Ryan McKendrick (both of George Mason University) with the opportunity to 'play' with truly mobile neuroimaging, they were excited. And they came up with an interesting experiment: testing the performance benefits of 'smart' eyewear.

Participants were asked to walk round a college campus using Google Glass or a handheld device with Google Maps, while wearing a functional near-infrared spectroscopy (fNIRS) headband for brain activity analysis (2). We asked Ryan McKendrick and Hasan Ayaz to tell us what they discovered when they took their neuroimaging technique to the streets...

Could you tell us more about fNIRS?

Hasan Ayaz: fNIRS is an emerging neuroimaging technique with a unique set of features that make it a good candidate for monitoring brain activity in natural settings. Specifically, it can measure localized brain activity in a similar way to functional magnetic resonance imaging (fMRI)'s blood oxygen level-dependent (BOLD) signal. When a particular brain area is activated, it requires more oxygen, and a surge of oxygen-rich blood is delivered immediately via neurovascular coupling. By tracking these tiny fluctuations, we can monitor activation of different areas, which is already proving useful in certain clinical and field applications.

Ryan McKendrick: fNIRS has low usage costs, and it allows for continuous data collection, so it works really well for longitudinal neuroimaging studies – and it is also incredibly quick to set up relative to other neuroimaging techniques. fNIRS is also very robust to motion, which is a huge benefit, considering our study took place while participants were constantly moving! Finally, because it is based on neurovascular coupling, we can leverage a lot of the basic research from fMRI in interpreting our data and developing theories.

Why did you focus on 'smart' eyewear?

HA: It gave us a unique opportunity to investigate how ambulatory systems, such as navigation aids, are used and how the brain engages during use in natural environments.

RM: Companies developing new technologies often focus on minimizing frustration for users, by maximizing intuitiveness and ease of use. These attributes are important and easy to test; however, if performance gains and integration with our neurobiology are not tested, we are missing a huge opportunity for societal advancement.

What did you discover?

RM: First, we found that a wearable display can give the user more cognitive reserves than a handheld device, so they can carry out other tasks more effectively. This may potentially lead to better awareness, integration and future projection of information from our surroundings. However, this benefit was diminished by improper display design. Google Glass simply imported its symbology from Google Maps, which may have been the simplest

solution, but it doesn't seem to have been the best. The issue was that Glass grabbed attention away from the environment, itself a well-known issue for heads-up and head-mounted displays. Had more attention been paid to designing the symbology for Glass around user behavior and brain activity, we believe Glass users could have blown away the phone users in our study.

What's next?

HA: I will investigate new emerging applications of fNIRS from medical to field applications. In particular, neuroergonomics and how brain imaging could be used to improve product design and user interface is intriguing. I believe this approach can be useful for many complex systems.

RM: I see neuroergonomics as a robust science for vetting new technology. My future work aims to solidify neuroergonomics as an adoptable toolkit within academia and industry, and grow the field via integration with other techniques from machine-learning and applied cognitive architectures, as well as pharmacodynamics and kinetics. I'm also looking at creating better models of in situ brain dynamics.

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1. *R Parasuraman et al., "Neuroergonomics: The brain in action and at work," Neuroimage, vol. 59, 1-3, (2012).*
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Instant Raman

A fiber-optic spectroscopic tool probes IBD – in real-time and in vivo

Approximately one in every 200 people has inflammatory bowel disease (IBD) (1). For sufferers, it's not just the pain and indignity of some of the disease's characteristic symptoms (abdominal pain, weight loss, diarrhea) they must contend with, but also the increased risk of gastrointestinal cancer – so appropriate disease management is key.

To effectively treat the condition, it's important to correctly diagnose the subtype – ulcerative colitis or Crohn's disease – but an overlap in symptoms makes the task difficult. In fact, there is only one (significantly invasive) way to avoid diagnostic uncertainty: colon biopsy (2).

In the past, researchers have investigated less invasive techniques such as laser endomicroscopy or MRI. Unfortunately, these methods focus on structural tissue changes, which are caused by IBD rather than being a symptom of it, making disease diagnosis less accurate.

Could Raman spectroscopy offer an effective in vivo alternative? A team of researchers led by Anita Mahadevan-Jansen decided that it was worth a shot (2). By coupling the technique with a fiber-optic probe, they created a real-time, minimally invasive tool to characterize the spectral signatures of IBD, reaching 90 percent sensitivity and 75 specificity to Crohn's disease. The method was also able to determine the severity of the disease.

By striking a balance between diagnostic accuracy and patient safety and comfort, the new tool could be an important first step toward a minimally-invasive, real-time clinical diagnostic for IBD. *WA*

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If I Could Turn Back Time...

Analytical scientists solve the mysterious case of the Finnish Clock

Measurement science can provide a wealth of information about materials, degradation pathways, and manufacturing techniques of historical artifacts, as well as assist with provenance studies and restoration monitoring. And if you want to analyze valuable or immovable artifacts in situ and with minimal destruction, portable Raman and X-ray fluorescence (XRF) spectroscopy are the tools of choice – which is why a collaborative team from Helsinki and the Basque Country used them to analyze the clock faces of a Government Palace in Finland's capital (1).

The two clocks were a dirty white when renovations of the palace began in 2004. Conservators were keen to restore them to their original color – but what was it? A research group at the University of the Basque Country (UPV/EHU) collaborated with Raili Laakso (a PhD student at the University of Helsinki) to find out.

Group leader Kepa Castro specializes in chemical analysis of cultural artifacts and the impact of environmental pollution on cultural heritage – steel sculptures, ancient ceramics in Pompeii, and wall paintings, to name a few. In this case, the Helsinki contingent wanted to discover the pigments used on the clocks over the years – and began to peel back history, layer by layer. The team analyzed cross-section samples to discover that multiple layers of paint have been applied to the clock faces over the years – but the original color was black.


West Face /VN1 (After restoration)


VN1


East Face /VN2 (After restoration)


VN2

Translating laboratory advances into field science has been a boon to cultural artifact analysis – and something that Castro says has only become possible in recent years. "With XRF, we can identify the elemental composition, with some limits – and this gives us an initial idea of the nature of the artifacts," he says. "Then Raman can be used in parallel to obtain the molecular composition." But Castro also notes that the in-situ approach has its limits: "We can only reach the surface of the artifacts with XRF, but in this case we needed to study the layers beneath, a stratigraphy – and, for that, sampling is indispensable." At this stage, they took the same scientific approach back to the lab, with the addition of scanning electron microscopy, Raman microscopy and infrared spectroscopy.

Castro believes that a combination of different analytical techniques is crucial for success. "All manner of analytical techniques have been applied in this field, from classical chemical tests to synchrotron radiation, but on very few occasions will the analysis of an artifact using a single analytical technique be really successful," he says. "Fortunately, we now have more access to standard analytical techniques – made possible thanks to improvements in technology, to the birth of computing, laser technology, sensoring, and so on. These things were science fiction in the 1950s!"

Visitors to Helsinki can now see the restored clock faces, just as they would have looked when the palace was built in 1822. *JC*

Reference

1. *K Castro et al., "Spectroscopic analysis used to uncover the original paint color of the Helsinki Government Palace tower clock faces", Herit Sci, 4, 36 (2016).*

Old Methods, New Tricks

Meet the tiny spectrometer that gives instant food analysis

What?

The NeoSpectra Micro is a chip-sized near infrared (NIR) spectral sensor, designed for 'on site' analysis. Measuring 18mm x18mm, and only 4mm thick, it is small enough to fit into existing mobile devices – potentially making it just as accessible to consumers as it is to industry.

Why?

The sensor was designed to test food safety and pharmaceutical purity but can also tackle the composition of environmental matrices, such as soil and water, according to the product's website (1). And its ability to offer analysis in minutes could be of significant interest to those charged with monitoring agricultural and pharma processes. It could also empower consumers to carry out their own food and drink analysis; for example, it has recently been combined with an iPhone app to detect caffeine levels in coffee (2).

How?

The chip utilizes NIR spectroscopy to analyze 1150–2500 nm – the highest yet for a spectrometer of its size, according to the company press release (2).

It comprises:

- MEMS (micro-electromechanical systems) chip: monolithic Michelson interferometer
- Photodetector: single element uncooled InGaAs Photodetector
- ASICs (application specific integrated circuits): for system control and data processing
- Sample interface: configuration of a light source for sample illumination, and a glass lid for free-space light collection

Who?

The microspectrometer was designed by Si-Ware systems; the spectral analysis algorithms were designed by GreenTropism.

What next?

As well as promising speedy analysis in food, agriculture, and pharmaceuticals, the NeoSpectra Micro could have further potential in healthcare – the sensor's size allows it to be integrated into wearable devices for biochemical monitoring. Will it live up to the hype? Watch this space.

References

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3. *http://www.neospectra.com/neospectra-micro/*

A Rare Find

Capillary electrophoresis triumphs in tracking down rare earth elements

Cell phones, lighting, wind turbines, military equipment… many modern technologies rely on rare earth elements (REEs). Comprising the lanthanide series plus scandium and yttrium, REEs are widely distributed in nature, but the challenge is finding sources that contain potentially useful quantities. Neutron activation and inductively coupled plasma-mass spectrometry (ICP-MS) methods have been the chief means of tracking down the elusive elements – until now. Three chemists from St Petersburg State University in Russia have developed an alternative for detecting and analyzing REEs more quickly, more cheaply and with good sensitivity: capillary electrophoresis (CE; Capel-105, Lumex) with UV detection (UV mini-1240 spectrophotometer, Shimadzu) (1).

"The greatest difficulty is usually the detection of ultra-microconcentrations of REE against the background of interfering components," explains Vitaly Nikonorov, a co-author of the related paper. "We discovered that co-precipitation of lanthanides with certain elements in the presence of polymeric carriers was the most efficient way to overcome these difficulties." Indeed, the team's optimized CE method was able to deliver detection limits ranging from 0.2 to 0.7 µg/L – much lower than achieved in previous research.

Nikonorov says the results help to disprove common misconceptions about the capabilities of CE. "Analytical scientists know that is much easier to develop a method than to adapt it to a real-world objective," he says. "It is often assumed that CE displays insufficient sensitivity for the determination of very low content of lanthanides in soils and waters, but it has proven itself to be quite competitive – demonstrating that reliable, responsible analytical practice should never be based on a single technique – however effective it may be." *JC*

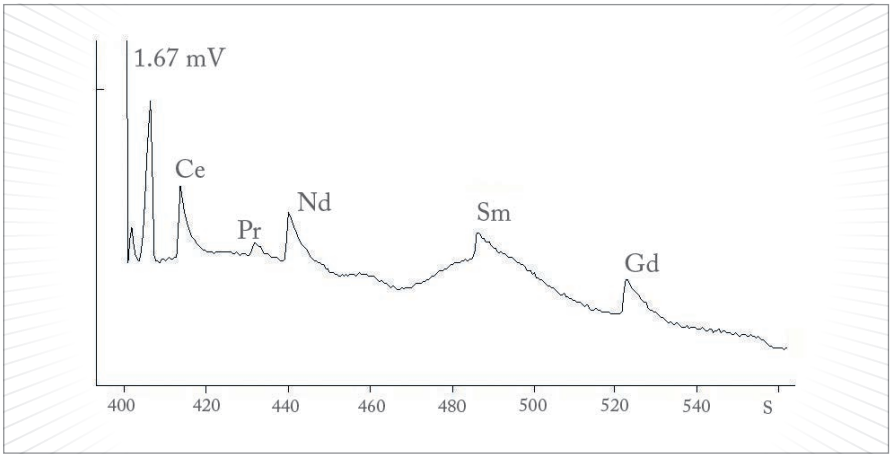

Figure 1. CE determination of REEs in tap water.

Reference

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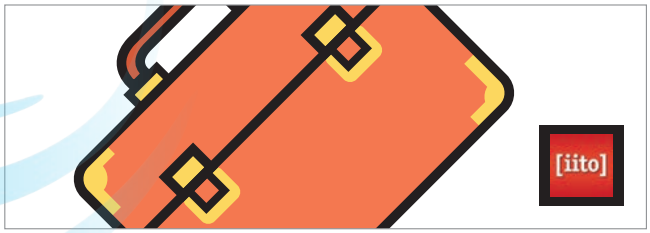
Diagnostics, Devices and On-Demand Data

What's new in business?



In our regular column, we partner with www.mass-spec-capital.com to let you know what's going on in the business world of analytical science. This is a busy month for collaborations and strategic alliances, with various companies partnering up to advance diagnostics and drug discovery.

Products

- Genedata launches on-demand data science services
- SCIEX launches X500B QTOF mass spectrometry system and new fast glycan labeling and analysis kit
- Consortium of TU Munich, JPT Peptide Technologies (JPT), SAP and Thermo Fisher Scientific announces PROPEL (ProteomeTools Peptide Library) and PROSPECT (ProteomeTools Spectrum Compendium)
- PerkinElmer launches NexION 2000 ICP-MS system
- Bruker releases Biopharma Compass 2.0 software

Collaborations

- bioMérieux and Banyan to develop blood-based IVD Tests for traumatic brain injury (TBI)
- Bruker microCT licenses iTomo image reconstruction software
- Thermo Fisher Scientific and Amerispec Diagnostics announce new LC-MS workflow
- Analytik Jena and Bruker present uHTS MALDI sample preparation for rapifleX MALDI PharmaPulse at SLAS2017
- AMRI, Bruker and HighRes: strategic alliance to advance mass spectrometry for high throughput screening (HTS)
- Lipotype GmbH is partner in new IMI project BEAt-DKD
- Thermo Fisher Scientific and ASTM develop IC-based water test method

Investment and Acquisitions

- PerkinElmer to acquire Tulip Diagnostics in India
- Bruker acquires nanoindenting company Hysitron Inc.

People

- Tecan appoints Klaus Lun as Head of Life Sciences Division
- Trent Basarsky joins 908 Devices as Vice President and General Manager of its Life Science Vertical
- German Merck appoints Anke Schenkel as Head of Group Controlling and Risk Management

Organizations

- SGS opens new consumer products testing lab in Vietnam
- Isoprime Ltd is changing its name to Elementar UK Ltd

For links to original press releases and more business news, visit the online version of this article at: tas.txp.to/0217/BUSINESS

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

Clinical Metabolomics: Will it Deliver?

Blindly searching for biomarkers in the metabolome has failed to deliver on early promises – it's time for a new direction.

By Martin Giera, Head of the Metabolomics Group at Leiden University Medical Center, Netherlands.

Numerous research articles have proposed, addressed and promoted metabolomics as one of the key tools for biomarker discovery and personalized medicine. Personally, I am not blessed with a lot of patience, but even those who are might be starting to wonder, "After more than a decade of metabolomics-driven research, can anyone actually name a single resulting biomarker routinely used in the clinic?" I have to admit that, besides trimethylaminoxide and some markers related to gene defects (for example, 7-dehydrocholesterol), nothing comes to mind.

But why? Have we not used the most advanced analytical and computational approaches available? Have we not invested enough money, manpower and dedication? I don't believe that lack of effort is the problem; I think we just took the wrong path.

In the beginning, when metabolomics was first used in case–control studies, it all seemed pretty straightforward. Many believed that with the right equipment and the right bioinformatics approach, we would easily identify some discriminators between all the molecules we can monitor. But the human body contains more than five liters of blood, we eat more than 500 g of (highly diverse) foods and drinks every day and, to make this picture even more complicated, our molecular fundament depends on genes, sex, weight, race and lifestyle. On top of all these variables, the metabolome is further influenced by circadian rhythm, hormones (mood), menstruation and medication. Say you are looking for a cancer marker – how are we going to find this one molecule, possibly secreted by a few million cancer cells somewhere in your brain or lungs, hidden in a constantly changing five-liter bucket of blood? Frankly, I am not convinced there is a high chance of success.

I don't want to paint too dark a view here, but simply illustrate that metabolomics biomarker discovery is a very complex endeavor. It's possible that our vision was blurred to the difficulties by the high hopes we had. Nevertheless, I am convinced metabolomics will make its way into the clinic, and hopefully fill the pipelines of clinical chemistry with new molecular

"I don't want to paint too dark a view here, but simply illustrate that metabolomics biomarker discovery is a very complex endeavor."

tools. In life, you have to fall and get up many times before you learn to walk, and it's time for clinical metabolomics to take two seminal steps forward.

The first step is to change our mindset – away from traditional biomarker discovery studies and towards understanding the systems effects of metabolites, as outlined in a recent article from Gary Siuzdak's lab (1). The second step is to define the framework of human metabolism. In other words, what are the actual (true) concentrations of metabolites, what is the range these metabolites are to be expected in vivo, and how are these concentrations affected by circadian rhythm, food intake, tissue distribution and many other factors?

Such steps are increasingly being taken in several recently established phenome centers. In my view, these are exactly the right steps, in the right direction, at the right time (if not a little too late...). Clinical metabolomics has learned from its past failures and too few successes, and is ready to start taking strides into the future.

Reference

1. *Johnson et al., "Metabolomics: beyond biomarkers and towards mechanisms", Nat Rev Mol Cell Biol, 17, 451–459 (2016).*

Credit Where Credit's Due

When is it right to claim journal authorship – and, more importantly, when is it not?

By John Griffiths, Senior Analyst at Hall Analytical Laboratories, Manchester, UK.

Under what circumstances should it be deemed legitimate to accept, or moreover to expect, authorship of an academic paper? The question has troubled me from time to time in my research career. The desire to publish is a prerequisite to a successful career for any student, researcher, principal investigator (PI) or professor. But to publish at any cost? Hopefully not. In today's highly competitive funding climate, the doctrine of "publish or perish" resonates more than ever with academics. Published papers and impact factors are the currency of research groups, and this is particularly applicable to postdoctoral researchers. For a postdoc, times are tough. Contract lengths of three years or less are standard practice, and in this snapshot period of their career, it is essential they publish (preferably as first-named or corresponding author) to demonstrate their capability and productivity to future employers.

So, what is required by an academic journal for a contributor to be rightfully acknowledged as a legitimate author? In my experience, the criteria seem to depend on the journal policy and on the individual editor; however, most appear to rely solely on the honesty of the corresponding author. Strictly speaking, the requirements are straightforward enough and are perhaps best summed-up by the recommendations of the International Committee of Medical Journal Editors (ICMJE) (1), which state that authorship should be based on four criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; *and*

- Drafting the work or revising it critically for important intellectual content; *and*
- Final approval of the version to be published; *and*
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

To make it crystal clear, all four requirements must be met in order to qualify for authorship. I do wonder how realistic this is – and how often it is adhered to in practice.

Personally, I would consider that a significant input into the work should suffice for acknowledgement as an author. However, I have encountered several situations where authorship expectations have been of a somewhat dubious nature – and where the ability to quote the above guidelines has been very helpful. On one occasion, a PI tried to insist that he should be a named author on a paper (to which he had had zero input) simply because one of his postdocs had contributed to it (and was named). Needless to say, the request was politely declined by referencing the guidelines mentioned above, much to his annoyance. In a similar vein, a professor claimed to have the right to automatic authorship on any of his staff's papers by virtue of them working within his group – not something that I, or most people, would probably sympathize with. I am also aware of a well-respected scientist who actually removed his postdoc's name from an article, which the postdoc had singlehandedly written, "for political reasons". I imagine most postdocs have similar tales to tell.

A (probably) more benign (and somewhat amusing) claim made by one professor of my acquaintance was that the order of authors' names on a paper – critical for citation purposes – had to be alphabetical. I guess that's OK if your name is Albert Aardvark, but a bit harsh on the rest of us. Needless to say, the professor had a surname much closer to A than Z...

I believe that no matter what guidelines are in place, the onus is on all of us to self-police the process of authorship, and to be comfortable in excluding names from papers, including our own, in the interest of integrity.

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Measuring the Microbiome

Untangling the complex web of relationships between humans and the trillions of microbes who share our bodies is a daunting task, but novel application of modern analytical techniques at least gives us a chance.

By Liam M Heaney, postdoctoral scientist in the Department of Cardiovascular Sciences, University of Leicester, UK.

The symbiotic relationship between humans and microbes is important for maintaining good health. And according to mounting evidence, dysfunctional relationships could increase susceptibility to disease (1). Here, I will use the example of trimethylamine [N-oxide] (TMA[O]), a molecule mediated through metabolism of dietary components by gut microbes, to illustrate the complexity of the microbiome.

TMAO can be measured in biofluids and, in 2011, was found to be elevated in the plasma of patients diagnosed with coronary artery disease (2). Later, it was demonstrated to be elevated in patients at higher risk of major adverse cardiac events (for example, stroke, myocardial infarction) within three years (3). Most systemically circulating TMAO is formed by metabolism of dietary components, such as L-carnitine and free choline, by the gut microbiota (4). These molecules are readily available in red meat and dairy, and TMAO has been identified as a possible mediator in the link between red meat and cardiovascular disease. But the relationship is complex. Paradoxically, TMAO is present in relatively high quantities in fish, yet populations with seafood-rich diets are considered at lower risk of heart disease than other western populations (5). We, and others, are attempting to unravel the relationship between diet, TMAO and heart disease.

TMAO is a non-volatile small molecule (molecular weight 75.11), and liquid chromatography-mass spectrometry (LC-MS) methods have been developed to measure circulating concentrations in plasma and serum, and excreted concentrations in urine. Though previous methods have predominantly employed multiple reaction monitoring on triple-quadrupole MS systems, our lab has developed a protocol employing the quadrupole-traveling wave-time of flight setup on a Waters Synapt G-2S instrument (6). The inclusion of a dilution step, using an isotopically labeled internal standard (D9-TMAO), allows a highly specific and selective analysis of samples with accurate quantification. Additionally, the inherent ability for selected/multiple reaction monitoring measurements using LC-MS allows for simultaneous analysis

of other molecules related to gut microbial metabolism, without loss of sensitivity or selectivity. For example, analyses may include additional molecules, such as L-carnitine, choline, betaine and γ-butyrobetaine, allowing an improved understanding of the dynamics and kinetics of these molecular/metabolic relationships.

Using these methods, we have shown that elevated levels of TMAO are associated with poor prognosis in acute hospitalizations of heart failure (7) and myocardial infarction (8). These experiments support previous data from gene knockout mice models, which showed that high levels of TMAO induced atherosclerosis (9) and worsened conditions associated with heart failure (for example, left ventricular ejection fraction) (10). Interestingly, we (and others) have also reported a strong correlation between circulating TMAO levels and markers of renal dysfunction. It is crucial that we ascertain whether elevated TMAO levels cause increased cardiovascular risk, or whether elevated TMAO is a side effect of renal dysfunction (11). In the latter case, increases in TMAO may be a surrogate biomarker for severity of cardiovascular/renal disease, rather than a direct cause. I'm confident that ongoing studies into the metabolic pathways involved will give us the evidence we need to establish the nature of these relationships.

Whether TMAO acts as a direct toxin on human cardiac/renal tissue or exists merely as a surrogate biomarker, this small molecule offers valuable prognostic information for a range of cardiovascular conditions, and we hope eventually to see it in clinical use.

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Window to the Future

One great discovery can start a chain of innovation – and a glut of patents. What do recent winners of the Nobel Prize tell us about the future of science?

By Andrew Rudhall and Mairi Rudkin, Chartered Patent Attorneys, Marks & Clerk.

Every autumn, the announcement of the year's Nobel Prize winners prompts us to reflect on the contribution to mankind of the discoveries and inventions recognized by the committee since 1901. Alfred Nobel established the Nobel Prizes when he wrote his last will in 1895, leaving the majority of his wealth to a fund that was to be awarded:

"to those who, during the preceding year, shall have conferred the greatest benefit to mankind."

Nobel himself was a prolific inventor and secured patent protection for 355 of his inventions, most famously dynamite. However, many Nobel Prize-winning discoveries are not patentable in themselves. Patent law distinguishes between a 'discovery' and an 'invention', and whilst it is possible to obtain a patent for an invention, discoveries in themselves are excluded. However, the practical application of a newly-observed phenomenon or discovery can lead to thousands of patentable inventions, often across multiple disciplines.

To obtain a patent, an invention must not only be novel but also industrially applicable. That is to say, it needs to have some sort of technical use. At the outset, the real-world commercial applications of a newly-discovered phenomena may not be immediately apparent, so there may be some lag between the initial discovery of a phenomenon and subsequent patent applications covering the technical devices and methods developed as a result.

For example, the Nobel Prize for Physics was awarded to Isidor Isaac Rabi in 1944 for the discovery of nuclear magnetic resonance (NMR). The development of NMR over the next seven decades is reflected in the history of the Nobel Prize and perfectly illustrates how a discovery in one area of science can have a profound impact on another. Indeed, the development of NMR techniques as a key characterization methodology in biology and chemistry was recognized by the Nobel Prizes for Chemistry in 1991 and 2002 and its use as a powerful diagnostic tool formed the basis for the 2003 Nobel Prize for Physiology and Medicine (awarded to Lauterbur and Mansfield for their research in magnetic resonance imaging (MRI)). At the time the prize was awarded to Lauterbur and Mansfield, MRI had become a routine diagnostic method and it was estimated that more than 60 million investigations using this technique were carried out annually worldwide.

Whilst it may not have been possible to patent the initial discovery of the phenomenon of nuclear magnetic resonance, the practical application of the technique has amazingly spawned over two million patent applications that refer to NMR and over 300,000 referencing MRI since 1944.

So what is the next world-changing discovery? In 2016, the Nobel Prize for chemistry was jointly awarded to Stoddart, Sauvage and Feringa for "the design and synthesis of molecular machines." A machine is essentially a combination of interrelated parts that are able to move relative to one another in order to perform a function. The work of these three chemists has provided the building blocks to synthesize machines on a molecular scale – based on the principles of supramolecular chemistry, in which a number of molecular units are assembled together.

"To obtain a patent, an invention must not only be novel but also industrially applicable."

Since their initial research was published, it has been become increasingly clear that there are a huge number of real-world applications for these molecular machines, including the provision of novel materials, sensors, energy storage devices and molecular robots. Consequently, there is no doubt this new field of molecular engineering will lead to many new patent applications.

The Nobel Prizes awarded in each of the three areas of science could be said to provide a window to the future, with the discoveries of today giving rise to the inventions (and patent applications) of tomorrow. In any case, given the history of the Nobel Prizes, it is reasonable to suppose that mankind can look forward to a plethora of technical and practical advances resulting from the discoveries and work of the 2016 winners.

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Analytical Science Sans Frontières

How a cross-border collaboration is empowering the African analytical community – and making a vital impact.

By Joanna Cummings

Whether political or geographical, financial or instrumental, each region has its own challenges. In many African countries, increasing student numbers and a dearth of instrumentation can mean little hands-on experience for the next generation of analytical scientists. But things are changing. Academics across the continent are increasingly teaming up with individuals, vendors and academic institutions in other parts of the world to reinvigorate teaching – a testament to the collaborative and supportive nature of the international analytical community. The ultimate goal? To create a well-funded and self-sufficient environment, where existing talent across the continent can be used to address key issues and deal with 'real world' problems.

We speak to scientists, students and the Royal Society of Chemistry to discover how the donation of an old GC-MS instrument has led to so much more...

FASTA Progress

By Steve Lancaster, Analytical Science Team Leader at Domino Printing Sciences, and co-founder of FASTA (Foundation for Analytical Science and Technology in Africa), St Ives, Cambridgeshire.

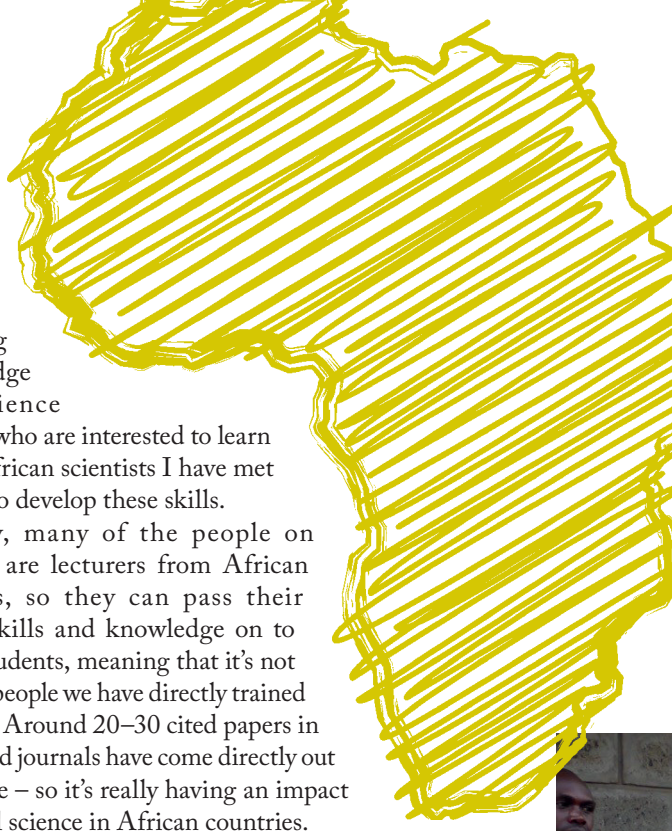
In around 2005, my former lab-mate, Anthony Gachanja – now an academic in Nairobi (Jomo Kenyatta University), contacted me to ask if I could find someone willing to donate a GC-MS instrument. He explained that many teaching staff were unable to provide their undergraduates with 'hands on' experience using advanced analytical equipment; mass spectrometers were simply not available. In addition, scientists in African countries have traditionally had to send samples away for analysis – either to South Africa, Europe or America. So as well as providing a good means of teaching students, having such instruments in situ would allow teaching staff to run their own samples – and that's really important.

I contacted Barry Nixon, who runs a company called Mass Spec Technologies, and he was able to donate one of their instruments; the lab was happy for it to go to a good home. We needed to raise about £3,000 to refurbish that instrument, ship it over to Nairobi and send an engineer over there to commission it. I was working at BP at the time, and they ran a 'matched giving scheme' – but we found out they could only double our money if we were a registered charity. So, in a nutshell, that's how FASTA came about – we became a registered charity in 2006. We raised the funds through sponsored events, had them matched by BP and were able to send the instrument over and commission it. Barry and I then went over to Nairobi and set it up.

Charting a course

Since setting up the mass spec in Anthony's lab, the Royal Society of Chemistry (RSC) has formed the Pan-African Chemistry Network (PACN), which works with universities, schools, scientists, teachers, and students to integrate African countries into international scientific networks. Training courses are a key part of the network, and I'm incredibly proud that the GC-MS training courses run by Anthony, Mathias Schafer (Cologne University) and me are perceived as the 'jewel' in the PACN crown.

We have now worked with around 200 chemists from all over Africa: mainly Kenya, Ethiopia, Uganda and Ghana, but people from as far afield as Nigeria and Egypt have also attended. It's rewarding to see people learning and developing confidence. I'm passionate about sharing my knowledge and experience with others who are interested to learn – and the African scientists I have met are hungry to develop these skills.



Crucially, many of the people on the courses are lecturers from African universities, so they can pass their newfound skills and knowledge on to their own students, meaning that it's not just the 200 people we have directly trained who benefit. Around 20–30 cited papers in peer-reviewed journals have come directly out of this course – so it's really having an impact on analytical science in African countries.

Together with GSK, we aim to increase the number of courses from two to about 10 per year by 2018/2019. GSK is investing heavily in Africa, setting up manufacturing facilities there, so they need a cohort of highly-trained analytical scientists.

Raising awareness, improving lives

We are also working with fellow scientists on projects in other parts of Africa, with a view to facilitating education – and, most importantly, improving lives through analytical science research. For example, we collaborated with a PhD researcher who was focusing on forensic analysis of wildlife (see "Vulture Shock").

The analytical science needs of Africa aren't as emotionally stirring as starving children – and that's how it should be. However, it does make it more difficult to raise money or awareness for analytical science projects. Many people don't understand what – or how important – analytical science is; it is almost invisible to people beyond the field.

The RSC and Domino Printing Sciences have been absolutely fantastic in facilitating a lot of this work – they've supported us, funded us, and have provided a lot of admin and managerial input. PerkinElmer and Shimadzu have been good enough to donate instruments, and Mass Spec UK have donated secondhand instruments through Barry Nixon. We are also exploring ways which we can work with Agilent. And the project certainly couldn't have grown without PACN, Syngenta and GSK. The passion of people on the ground is great, but without the backing of big organizations it's hard to have the same impact.

And the original GC mass spec? It's quite old but it's still in use in Anthony's lab in Nairobi. They've now got a couple of more modern instruments, but the original is still doing good service in teaching labs – all in all, it was a good investment!

Top to bottom: Delegates from the Ghana 2015 workshop; Steve Lancaster and colleagues at the Nairobi 2016 GC-MS course; Anthony Gachanja of JKUAK with Steve Lancaster and Jacob Midiwo of the University of Nairobi; Steve and colleagues raising money for FASTA.

Vulture Shock

By Steve Lancaster and Ngaio Richards

Vultures may not be the most beautiful of birds, but they fulfill a critical role in African ecosystems, and their declining numbers on the continent are a major concern. In India, the number of vultures has dropped by over 90 percent in the last 20 years or so, and Africa is going the same way – it's alarming. One major reason is that farmers occasionally need to give their cattle non-steroidal anti-inflammatories (NSAIDs) – the veterinary version of Ibuprofen – so they can continue to work, pulling ploughs. These NSAIDs are very toxic to birds, so when farmers leave cattle carcasses out to be picked clean by the vultures – so they can use the bones to make fertilizer – the vultures eat the flesh and die. It's resulting in big losses in the vulture population. There's another reason too: farmers whose cattle are taken by large predatory mammals, such as lions, sometimes leave poisoned meat out to kill the lions, which kills the vultures as well.

In one of our first projects in collaboration with African scientists, we worked with Ngaio Richards, a PhD student using mass spectrometry to measure the metabolites of toxins in vulture feathers and talons. Obviously, if a dead vulture has been out in the African sun for any length of time, the flesh is not a viable sample, so it's very difficult to analyze, but toxins can be analyzed in the feathers for some time after. We helped to develop methodology to measure these toxins, to build up a deeper understanding of why vultures are in danger of becoming extinct. These methods are now providing real forensic evidence. That, in turn, is feeding into an education program, so farmers and vets are much more aware of the need to be careful with prescriptions to animals – and also to be mindful that they're poisoning more than lions and tigers.

One big problem? Vultures are not highly thought of, so it's a hard sell – which can also be true of analytical science!

Empowering the Talent Pool

By Helen Driver, Senior Program Manager, Africa, at the Royal Society of Chemistry, Cambridge, UK.

GC-MS is a powerful way to analyze a range of substances – it can be used in everything from environmental monitoring and food safety to forensic science and medicine. When we decided to develop the course program started by Anthony Gachanja and Steve Lancaster, we were in a very fortunate position, as the expertise and equipment already existed in Africa. However, there is still a distinct need to increase the number of African scientists and institutions who have the skills to fully benefit from this powerful analytical method. We knew we needed to scale up the volume and impact of these courses to benefit more people – and as of now, we are on target to train over 400 African scientists by 2020.

Ethiopia, Kenya, Ghana and Nigeria are all experiencing ongoing growth in the quality and quantity of scientific research taking place. These countries operate as 'Hubs', engaging with people from other countries in their regions. The Pan Africa Chemistry Network (PACN) has been based at these four Hubs for many years, and the universities have the people, equipment and facilities needed to host the courses. In 2016, the four courses have trained people from ten different countries, including Burkina Faso, Cameroon, Sudan, Tanzania and Uganda.

The Hubs are a vital part of this program. When Anthony

Left to right: Anthony Gachanja; Caro Chepkirui and colleague; the RSC's Helen Driver speaking about the project.

Gachanja and Steve Lancaster started their small training program in Nairobi in 2006, budding analytical chemists traveled from across Africa to take part. Now that we have courses running across Africa, more people can attend the course in their home or neighboring country, limiting the travel required. We have worked hard to widen our advertising for the upcoming courses, to give as many people as possible the opportunity to be part of it. One big challenge we face is how to manage the demand for these courses; we get many more applications to attend than there are spaces available. However, we hope that over the coming five years we can start to meet that demand.

Widening horizons

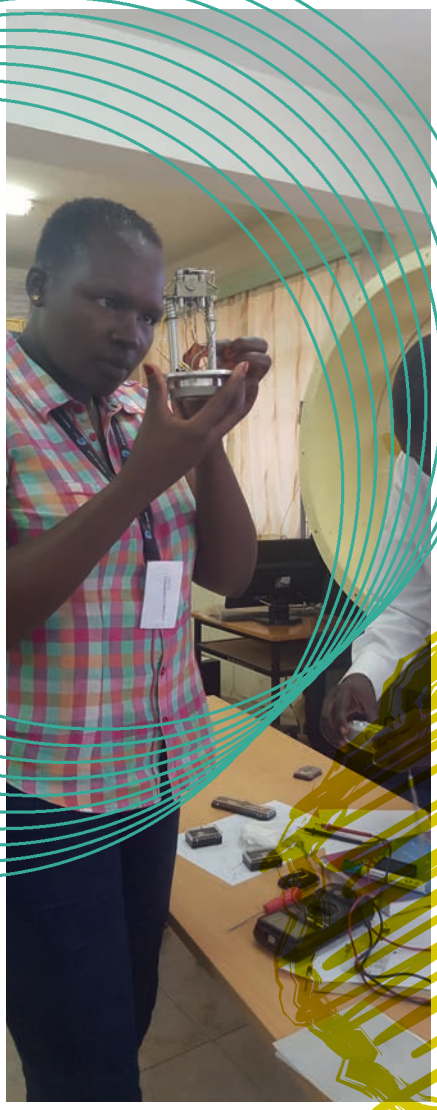
The project is a partnership between the Royal Society of Chemistry's Pan Africa Chemistry Network (PACN) and GSK. We have been keen to roll this program out across Africa for many years, and support from GSK has enabled us to do this. The PACN shares many objectives in common with GSK's ambitions and investment in Africa. We are both working to ensure sustainable scientific development in Africa by equipping local scientists with the skills, knowledge and training they need. GSK supports their staff to engage in volunteer opportunities, and so far, five members of GSK staff have been confirmed as part of the project, sharing their specialist analytical expertise with us.

In fact, everyone who is part of the programis a volunteer, putting in a lot of time and effort to ensure that the courses benefit Africa's future – the enthusiasm and dedication of delegates and trainers alike have been essential to the success of this program. The delegates and trainers spend time learning and socializing together and form a strong, supportive community – and those links will help support the delegates after the course, once they return to their home institutions. It is an exhausting, but highly rewarding week for all those involved!

"Teach a man to fish..."

So far, all the previous courses have been run by Anthony Gachanja and one international trainer (for example, Steve Lancaster, Mathias Schäfer from the University of Cologne, Imran Janmohamed from Anthias Consulting, Steve Lancaster from Domino Printing Sciences and a selection of volunteers from GSK sites in the UK); however, this is not a sustainable model. Local colleagues need to feel empowered with the skills and knowledge to be able to run these training courses in the future. We are focusing on the local trainers and supporting them in their journey to become regional experts in GC-MS, which should enable them to then train other scientists. Each of the four Hubs has nominated at least two colleagues for this role and they are already taking an active part in the courses as part of their training. For example, Ray Voegborlo from KNUST in Ghana ran many of the practical sessions in the training course earlier in 2016 and Dr Estifanos from Addis Ababa University in Ethiopia is already rolling out the training course to other universities in the country. Such individuals will ensure sustainability of the training into the future.

Ultimately, our aim is to strengthen local training capabilities, giving the science community a sustainable base on which to develop the skills needed by companies, governments and institutions. It's about investing in the talent pool. We have plans to expand the training into other analytical methods and we are currently exploring which other techniques would be most beneficial to African science. It's a key part of our efforts to help scientists in Africa acquire the information, skills and professional connections they need to tackle the challenges facing their societies.



Clockwise from top left: Caro with young chemists at Sacred Heart School, Nairobi; Caro with participants at GC-MS training, JKUAT, Nairobi; Caro assembling a mass spectrometer.

Standing Tall

"Because of the workshop, I can now handle GC-MS without fear!"

By Caro Chepkirui, Head of Department, Sacred Heart School, Nairobi, Kenya.

Raised in the villages of the agriculturally-rich Rift Valley region of Kenya, I developed a love for farming, despite the often monotonous nature of the work. Once I came of age, it was routine for me to accompany my parents to the farm – to till the land, clear it of weeds or combat pests. I noticed that pest infestations would cause dwindling yields, much to the disappointment of my parents – and to all of us who worked so hard to reap the best harvests. As I progressed through high school, I had to sacrifice much of my precious school time to deal with pest infestations, and this drove me to investigate more effective (and less tedious) means of preventing pest attacks on our crops.

I began by using naturally available components, like ash from firewood and concoctions from various weeds and herbs for application to crops on the farm. I was delighted to find that some of those remedies actually killed the aphids and cutworms (moth larvae) on affected plants! This not only inspired me, but also really fascinated me – it kindled an insatiable desire to establish the chemical composition of my concoctions. And I made it my priority to create and test my innovative pest control strategies.

I participated in all the science congresses I could during my secondary schooling. It didn't take long for my chemistry teacher to notice my interest in the subject and encourage me to pursue and hone my analytical skills. This was replicated in my university education. My passion for analytical chemistry, as well as my teachers' guidance and encouragement, have allowed me to reach where I am today.

My current research leans heavily towards analytical and environmental chemistry. I am researching the use of geosorbents in the degradation of pesticides; more specifically, pesticides that cause adverse environmental pollution. Even though global usage of persistent organic pollutants (POPs) is restricted and some have now been totally banned from the market because of their adverse effects, their presence in the soil matrix is still very pronounced. Geosorbents are able to bind to other pollutants of a similar nature because of their high cation exchange capacity.

I learnt about the Royal Society of Chemistry training course via a member of teaching staff in the chemistry department at the university. I hurried to apply, and when my application went through, I couldn't wait for the day to come. It was a Godsend, coming at a tumultuous time in my research; a time when I was experiencing challenges with the use of gas chromatography (GC) in my analysis. Therefore, I hoped to gain both theoretical knowledge and practical skills in the use of gas chromatography-mass spectrometry (GC-MS) at the workshop. The training surpassed my expectations. Not only was I able to solve some of the challenges I had earlier experienced, but I also learnt a great deal of new information. Memories of the practical sessions of dismantling and assembling parts of the mass spec machine remain fresh in my mind. And the skills I acquired gave me the confidence to handle GC-MS (as well as GC-electron capture detection) without fear...

It was an eye-opening experience. During the training, I went through step-by-step preparation of samples; sample clean-up using a solid phase extraction technique, manual injections on the GC-MS, all the way through to analyzing data from the print out spectra. Using what I had learnt and the hands-on experience, I re-analyzed some of the samples I had already run and the results were much better. I feel I have an improved understanding of what I'm doing – and the troubleshooting lessons help me a great deal whenever I encounter an error. Before the workshop, I did my analysis like an airline pilot heading for an unknown destination – but without knowing how to fly or navigate! The workshop equipped me with the skills to get to where I want to be.

Most scientists in Africa, and in Kenya in particular, are theoretically knowledgeable but lack the requisite practical skills for addressing African challenges through science. Rolling out this program across Africa is important; it empowers the continent's scientists with suitable knowledge, capacity development and practical skills to be able to solve problems. I would not hesitate to recommend this program to other scientists wanting to get a head start.

The best way to learn something is to learn from the experts, but the best way to retain the contents is to teach others, which is exactly what I will set out to do when an opportunity presents itself. I have so far established a group of young chemists (secondary school level), who I mentor to further the RSC's noble initiative. I spend my free time talking with them about the impact of chemistry on day-to-day living and, in turn, they tell me their future aspirations. So far, these young chemists have demonstrated a growing interest in and passion for chemistry – and greatly improved their grades in school. I am convinced that they will become better analytical chemists in the future as a result of my mentorship.

My experience with the RSC has been one-of-a-kind in my academic journey. I have become a better analytical chemist and I feel like I can now stand tall among other chemistry academics.

Equipped for Progress

"Holding GC-MS training workshops across Africa will help build capacity in research institutions across the continent."

By David Azanu, Lecturer and PhD student at Kumasi Polytechnic, Kumasi, Ghana

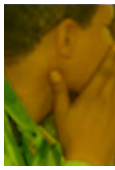
Back in 2007, I was a teaching and research assistant in the Department of Chemistry at Kwame Nkrumah University of Science and Technology. I helped to teach analytical science to the third and final year undergraduate students and contributed to research and consultancy work performed at the analytical instrumentation section of the department. Together, these roles aroused my interest in learning more about analytical science. I'd learnt about the theory of GC-MS during my undergraduate work, but hadn't had any hands-on experience. I believed (and still do) that analytical science could be used in Ghana to address issues such as the adulteration of food, discovery of novel drug leads, and environmental testing for emerging chemical pollutants (endocrine-disrupting compounds, for example).

When I applied for the GC-MS 2016 workshop at KNUST, I was hoping to refresh my theoretical knowledge and gain hands-on training on GC-MS. I also wanted to learn more about troubleshooting and fault identification.

And I was not disappointed. I learnt a lot at the workshop, such as how to cut a capillary column, how to dismantle and assemble the ion source – and, of great personal use to me, how to identify the best sample preparation technique to use for flavonoids in my current work on chili peppers. I now understand spectra and can better interpret them. And when running GC-MS, I'm now able to identify basic faults and implement troubleshooting approaches.

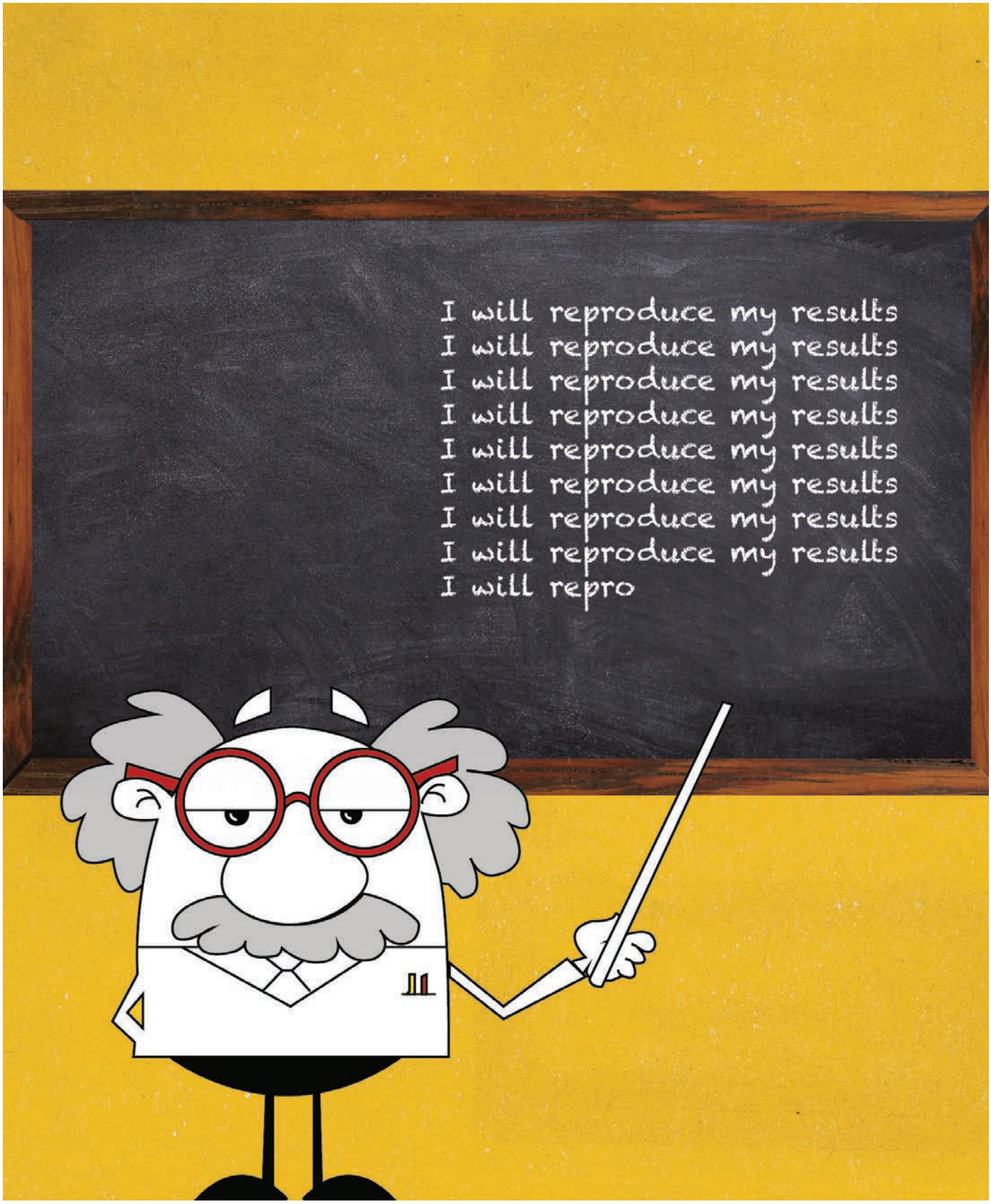
Since the course, I've been part of two highly successful DANIDA- and NSF-sponsored projects; Safe Water for Food and Climatic Extremes, Mining, and Mycobacterium Ulcerans: A Coupled Systems Approach (ReBuilD). Additionally, I've worked on a Commission on Human Rights and Administrative Justices (CHRAJ) Project, which focused on human rights in mining communities. Through working on these projects, I have co-authored nine papers published in peer-reviewed journals.

The current interests of my research group include: i) environmental testing for emerging chemical pollutants (endocrine disrupting compounds, antibiotics, antibiotics and steroids); ii) eco-toxicological modeling of emerging chemical pollutants; iii) natural dye enhancement for use in the textile industry in Ghana. And, as noted above, I am also working with a colleague to identify volatile (flavor) compounds in chili peppers grown in Ghana.



The workshops have undoubtedly helped me further my own research, and have given me opportunities I may not otherwise have had. I believe the major factors affecting African nations are a lack of state-of-the-art equipment, a lack of expertise in handling that equipment, and an underdeveloped network or platform of analytical scientists to share and discuss issues. To me, holding GC-MS training workshops across Africa will help build capacity in research institutions across the continent – it's a great step towards equipping Africans for progress in the analytical sciences.

Clockwise from top left: David Azanu (center, in floral shirt); Steve Lancaster; Caro Chepkirui and colleague.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CARE To repeat THAT?

Today's scientific literature appears to contain an inordinate number of irreproducible papers. Why? And what should we analytical scientists – the bastions of reproducibility – do about it?

By Ira Krull

Over the years, my colleagues and I have amassed a large number of columns, review articles and even books, all dealing with various aspects of analytical method validation (AMV). If one types these three words into a Google search, around 4.33 million results will pop up. It appears to be a very popular area of analytical chemistry. But what has this to do with much of today's scientific literature (especially in the biological and medical sciences) appearing to be of questionable reproducibility (1–11)? Where is this apparent lack of generic reproducibility coming from and how can it be rectified in the future? These are worrying, pressing and, as of yet, not fully addressed questions. And I have many, many more for you...

Much has been written on these subjects but there seems to be some confluence of AMV, reproducibility/repeatability, and publishing poor science in general. Why? And where do the scientific journals (of all types) come into the picture, if at all? Should the burden of responsibility be on authors, journal reviewers, funding agencies, editors, peer review processes, graduate students, postdocs, or elsewhere?

REVIEWING REVIEWS

As a reviewer of (mainly) analytical papers for several decades, I receive too many papers that contain little-to-no true AMV, and no serious discussions of the topic – most of the data are single points with no evidence of any repeatability or reproducibility (n=1). There is, of course, rarely any statistical treatment of said data because there is simply not enough. How is it possible that such manuscripts even reach a reviewer (via the editors)? Why would anyone submit such a manuscript for serious consideration by a reputable journal? Why do some reviewers accept such data, allowing the paper to be published, requesting only minor revisions but no added data or studies?

INHERENT HETEROGENEITY OR INHERENT LAZINESS?

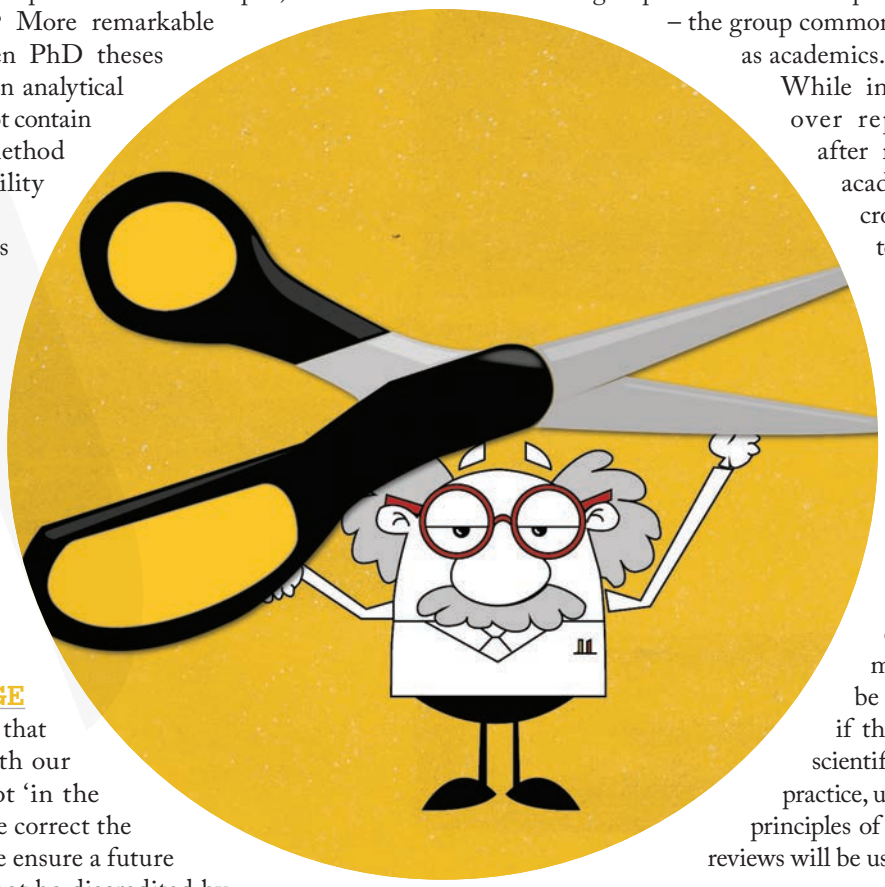
Antibody-based publications appear to demonstrate the very least reproducibility of all analytically-oriented papers. Antibodies, being proteins, often vary from source to source, as a function of how they were expressed and purified – perhaps this is the source of some irreproducibility in such papers/journals, but I believe most of the blame lies squarely at the door of researchers themselves.

As a practicing academic with an active research group for decades, I was always amazed by how few academic colleagues demanded that their researchers, graduate students, postdocs, visiting scientists, and/or undergraduates learn as much about AMV and the demonstration of repeatability and reproducibility as possible – and demonstrate it in all of their studies. It was (is) as if they never considered such behavior as an important part of doing quality research or publishing high-quality papers.

Even if the antibodies themselves are not reproducible, good method validation would prove the fact – in addition to indicating the reproducibility of the overall research. If such studies are not pursued or demanded by editors or reviewers, then more and more

papers will eventually and inevitably be shown to be irreproducible – which is exactly where we currently find ourselves. Is it possible that biologists are never taught anything about AMV? If so, is it also possible that research advisors and mentors do not require their students to know about this field or push them to work harder towards credible publications in the open, scientific literature? More remarkable is the fact that even PhD theses specifically focused on analytical chemistry often do not contain evidence of true method validation, repeatability or reproducibility.

All of the above leaves me with a big question mark over the reproducibility of the vast majority of papers appearing in analytical journals. Should we discount everything with little to no AMV? In any case, we need to find and fix the underlying problem.



TIME TO CHANGE

I think it's fair to say that the problem lies with our own efforts, and not 'in the stars'. But how do we correct the problem? How do we ensure a future where science will not be discredited by the suggestion that most of its publications are just not reproducible or useful? I think we can all agree that if even the originators of a piece of research cannot reproduce their findings, future researchers will also struggle... and that means everyone is just spinning wheels, wasting time, energy, hope, money and the future of science.

Suffice to say, everyone who publishes any type of science (or engineering for that matter) should be required to demonstrate – in the very first publication using such methods – complete AMV. There is no excuse not to. The field has now been perfected; it is used throughout the pharma/biopharma industries, it is a major part of ICH and all regulatory guidelines around the world for such products. Indeed, scientists in any industry that is regulated by a government agency (whether FDA, EMA, JPA or others) must validate all analytical methods or they cannot submit a chemistry, manufacturing and control (CMC), investigational new drug (IND), new drug application (NDA) or any other request to file and market pharma/biopharma products. However, complete AMV has never really been accepted, respected or adopted by the major group of scientists who publish scientific articles – the group commonly known as academics.

While industry scientists toil over replicate experiment after replicate experiment, academics bear no such cross. They simply need to convince the journal editors, peer reviewers, and funding agencies that their work is analytically valid and reproducible. The burden of the cross has been passed on, in our current system, to the journal editors and peer reviewers who determine if a given manuscript is ready to be published or not. And if these gatekeepers of all scientific literature also fail to practice, understand or utilize the principles of true AMV, then their reviews will be useless or worse.

BETTER GATEKEEPERS OR BETTER GATES

We clearly need gatekeepers who understand the science being presented, as well as the method validation requirements that must be met before any manuscript can be accepted for publication. Editors must also take responsibility in all of this mess by requiring, before any kind of peer review, that all manuscripts demonstrate full and complete method validation data, to the standard required of pharma/biopharma submittals to the FDA/ICH and most other regulatory agencies. Why should journals be any different than the regulatory agencies in what they expect of their publications? Perhaps journal editors are afraid to demand such a fundamental requirement of all submittals because they may not have a sufficient number of acceptable papers for the next issue...

There could be a more conspiratorial flaw in the peer review

process. If all reviewers simply accept manuscripts without any real validation data, their own submissions are consequently less likely to require such data. Let's hope that the entire system is not so rotten. But it would be very interesting to know how many publications (in any area of science) with analytical data are accepted without evidence of true and (perhaps) complete method validation data. It would certainly account for the apparent lack of reproducibility in so many different areas of science today.

I've asked many questions. And now you are most likely thinking: "OK Ira – you've made your point – but how do we rectify the problem?" Rectification comes with due diligence from everyone involved, and in having QA/QC procedures for this assurance. Journals must establish required guidelines for all future submissions. To a large extent, both Nature and Science now have such guidelines in place – better late than never (12). Such guidelines have been designed to ensure that everything needed to reproduce the work involved is present and that sufficient AMV studies are also indicated and verified. However, if the authors are not made to abide by these guidelines, then we cannot move on from the present impasse. Hence, editors and peer reviewers must enforce the guidelines; if the prerequisite AMV material is not contained within the text of the manuscript, then the paper should be rejected outright or accepted pending further revisions, to fully meet the guidelines. If the authors then fail to provide the information required to meet the guidelines, the manuscript must be rejected. 'Guidelines' is perhaps the wrong word to use for academics, as it may imply some degree of freedom – 'mandatory rules' may be better. In any case, it should clearly be the responsibility of the editors and (especially) the reviewers to ensure suitable and adequate AMV for all accepted manuscripts.

WE CAN DO BETTER

We find ourselves at an unprecedented point in the history of publishing scientific articles, and of science itself: the majority of papers in certain areas cannot be easily reproduced. We have arrived at this terrible juncture because we have been far too lax in what was – and is – required to publish in reputable journals, especially regarding AMV. And though journals may guard the gates, academic institutions and the academics within them have a big role to play. I believe mandatory undergraduate and graduate courses in AMV would make a difference – and at the very least, mentors and advisers should coach best practice in AMV and expect no less. Funding agencies should not take a back seat either, but deny future funding to those researchers who refuse to perform or report AMV in their papers.

I look forward to a future where peer reviewers begin to assume responsibility for rejecting manuscripts because of a general lack of AMV; where students no longer gain an advanced degree without knowing a great deal about AMV or how to apply it in the real world; where scientists and their students take AMV seriously, and thereby avoid publishing irreproducible papers that result from work that was never demonstrated to be reproducible in the first place.

Finally, we analytical scientists should be setting the very best example. If we aren't taking AMV seriously, how can we expect scientists in other disciplines to do the same? Don't be afraid to offer guidance when you're involved in a collaborative project that is going 'off the rails' – other members of the team may not be as well versed in the need for AMV. And don't be afraid to stand up and decry research or publications that fail to meet even the basic requirements for reproducibility. The whole of science is at stake.

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Murky Waters

Pharmaceuticals are slipping through processing safety nets and into our water systems. It's a growing global problem and cause for consternation – contamination from medicines may prove to be a defining environmental issue of our time. But how can we monitor and remove drugs from our rivers, lakes and drinking water?

By Melanie Voigt, Anika Gold, Christina Blaesing, Timo Hoelscher and Martin Jaeger

Our work on pharmaceuticals in wastewater started small. Spurred by warnings from both the media and scientific experts about the dangers of pharmaceuticals entering our water supplies, we initiated a student laboratory project to collect water samples from a nearby river, downstream of a wastewater treatment plant. We fully expected to find nothing – assuming any drugs would be removed during processing at the plant. Nevertheless, we conducted a few concentration steps using simple solid-phase extraction cartridges and ran some HPLC-ESI-QTOF-MS experiments. To our great surprise, tens of compounds were very easily detected. Both the number of drugs and the ease of detection struck us, so we decided to continue our research more systematically.

An extensive literature search confirmed that pharmaceuticals in the aquatic environment are a global problem, but published studies on the phenomenon are patchy (Figure 1) – and the quest for solutions is ongoing. Many details remain unsolved. Which laboratory conditions can best model the elimination? Which conditions are most efficient? What solutions can be scaled up for wastewater treatment? Which solutions are economically feasible?

Degrading drugs and feminine fish

Pharmaceuticals used in human and veterinary medicine find their way into wastewater in a number of ways. If the active ingredient is not fully absorbed in the human or animal body after administration, the compound is excreted, enters the sewage system and eventually arrives at a wastewater plant. Drugs that are absorbed are excreted in the form of metabolites, and enter the same water circulation routes. Individual disposal via household waste and wastewater has little importance for the entry of drugs into the environment, but hospital wastewater exhibits a high concentration of pharmaceuticals (1–3). All wastewater streams are usually channeled to the same conventional sewage treatment plants. And though they have mechanical and biological purification stages, such plants are often unable to eliminate pharmaceutical drugs, specifically antibiotics, from wastewater circulation (4–7). Wastewater plants may even concentrate the compounds as a consequence of the residence time within the plant. Usually, sewage treatment effluents are conducted into rivers, and the sewage sludge will be used as fertilizer in agriculture, allowing entry into groundwater. Furthermore, industrial wastewater from pharmaceutical plants can also lead to an increase of water pollution (8, 9).

The number of studies on the occurrence of pharmaceutical compounds in surface and ground waters has tripled during the last decade. The typical concentrations of active compounds and their major metabolites are low, in the microgram/liter range

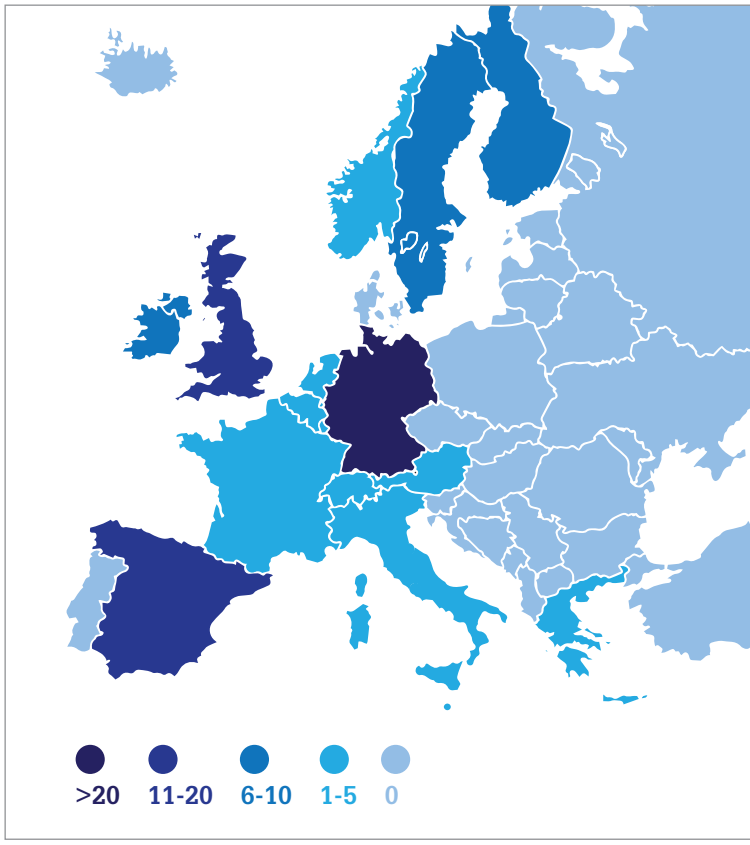

Figure 1. Publications on pharmaceuticals in European waters during the last decade.

(10–13) – well below the therapeutically effective threshold for humans. However, the consequences in the aquatic environment are severe; for example, feminization of fish, loss of diversity, and even extinction of species. In fact, drug residues and their metabolites can be found in all compartments of the aquatic environment (14–16).

The effect of drugs on the environment primarily depends on the degradability of the individual compounds. Biodegradation is influenced by many factors, such as pH value, temperature or further matrix properties, and is of great importance; the destruction of the synthetic chemical compound relies mainly on bacterial metabolism, degradation and eventual mineralization. However, photolysis, hydrolysis, and chemical reduction may all contribute to the compound's fate.

For humans, the consequences of continuous exposure to many drug substances are largely unknown. The concentrations of active ingredients of most pharmaceuticals in surface water, groundwater and drinking water are thought to be too low to cause toxic effects in humans. But the effects of long-term, low-dose administration of many drugs are not well (or easily) studied, so it's hard to say with any certainty.

Direct toxicity is not the only potential impact. One of the greatest problems facing human and veterinary medicine is the emergence of antimicrobial resistance (AMR). Primary antimicrobial resistance occurs frequently in nature; for example, the resistance of Pseudomonas aeruginosa to penicillin G. However, secondary resistance results from the contact of microorganisms with antibiotics. Bacteria can then share the genes for resistance via extrachromosomal genetic material passed on by conjugation. The resulting resistant bacteria may find their way into the environment and adversely affect aquatic and terrestrial organisms. Eventually, they may reach humans via the food chain. As the occurrence of antibiotic-resistant bacteria becomes increasingly frequent, our armory of effective antibiotics shrinks (17). Is massive entry of antibiotics into open waters via wastewater and effluents of wastewater treatment plants a contributing factor to antibiotic resistance? The jury is still out. Interestingly, urban wastewater has a similar number of resistant bacteria as hospital wastewaters with a high level of antibiotics (17). Even in urban wastewater with low concentrations of antibiotics, multiresistant E.coli, Acinetobacter, Enterobacteriaceae and Pseudomonas were detected. This finding could suggest that the emergence of resistant bacteria is actually caused by bacteria already rendered resistant by prior antibiotic treatment (17) rather than antibiotics in the environment, but is by no means definitive.

Stemming the tide

In our quest to reduce the entry of pharmaceuticals and their metabolites into the aquatic environment, we focus on the photo-induced degradation of active pharmaceutical ingredients. Using UVA and UVC irradiation in combination with a batch reactor, we have investigated the effect of pH, chemical additives and catalysts on degradation. By studying the structure of the phototransformation products and the velocity of the degradation, we can assess the efficiency of the conditions and catalysts chosen and, in doing so, discover the most effective combinations. We also investigate the chemical kinetics not only of the main compound, but also of its degradation products.

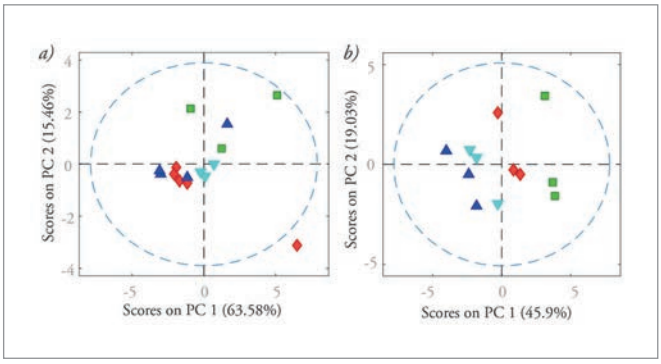

Figure 2. Score-plot showing that classes of antibiotics react similarly to variations of experimental conditions: fluoroquinolones, red diamonds; macrolides, green squares; sulfonamides, blue triangles; tetracyclines, light-blue triangles. (a) Score-plot showing that variation of experimental conditions causes changes in reaction rates increasing from left to right on PC 1. Conditions were: UVC-irradiation in the absence of oxygen and H_2O_2 (blue triangles); in the presence of oxygen and absence of H_2O_2 (light-blue triangles); after addition of 10 mg/L H_2O_2 (red diamonds); after addition of 30 mg/L H_2O_2 (green squares). (b) Briefly, the presence of oxygen and H_2O_2 accelerates the degradation of antibiotics during UV-irradiation.

We mostly rely on high-performance liquid chromatography (HPLC) coupled to high-resolution and/or higher-order mass spectrometry (MS). A linear ion trap and a quadrupole time-of-flight mass spectrometer equipped with electrospray ionization sources are our instruments of choice. Fragmentation techniques and accurate mass determination elucidate the structure of the degradants, while the time-of-flight analyzer ensures unbiased identification of all analytes in a water sample. We quantitate the results using the mass area, which is usually considered representative for the analyte concentration. Nevertheless, it is important to note that the ionization efficiency of an analyte is compound-specific and also dependent on the experimental conditions, particularly on the solvent composition at the retention time. We test the concentration–time (more precisely, the mass area–time) curves resulting from HPLC-MS analysis during an irradiation experiment against different kinetic models, to obtain the reaction order, degradation rate constant and corresponding half-lives of educts and products.

The toxicity of degradants can be predicted on the grounds of their chemical structure and known structure–activity relationships, but we also conduct toxicity assays. Our ultimate goal is to ensure complete mineralization of a compound, so that no potential for environmental harm remains.

Testing the Water

Environmental campaigning organization Changing Markets recently published a report uncovering widespread antibiotic resistance in wastewater from pharmaceutical plants in India (1). We spoke to the group about why – and how – the industry should address this important environmental issue.

Why focus on antibiotic pollution?

Pollution from antibiotic manufacture is known to be a factor in the global spread of drug resistance, alongside excessive consumption of antibiotics in human medicine and their profligate use in livestock rearing. This is still a relatively unexplored issue, despite a substantial and growing body of scientific evidence highlighting the negative environmental and human health impact of antibiotic residues.

In 2007, a team of Swedish scientists analyzed pharmaceuticals in the effluent from the Patancheru Common Effluent Treatment Plant (CETP), a plant serving about 90 pharmaceutical manufacturers on the outskirts of Hyderabad. The pharmaceutical concentrations in some of the water samples were higher than those found in the blood of patients taking medicine. The concentration of ciprofloxacin, a fluoroquinolone antibiotic, was approximately one million times greater than the levels found in treated municipal sewage effluent (2).

What did your investigation reveal?

Our report exposes the occurrence of resistant bacteria surrounding pharmaceutical manufacturing plants in India, which supply European and US markets. An on-the-ground investigation by the investigative agency Ecostorm and subsequent analysis of water samples under the supervision of Mark Holmes from the University of Cambridge found high levels of drug-resistant bacteria at sites in three Indian cities: Hyderabad, New Delhi and Chennai. In total, out of 34 sites tested, 16 were found to be harboring bacteria resistant to antibiotics (see right for breakdown).

Ecostorm Investigation: Results

34 sites were tested in Hyderabad, Visakhapatnam, Delhi and Chenna, India.
16 sites harbored antibiotic-resistant E. coli bacteria:

- 4 with resistance to cephalosporins, carbapenems and fluoroquinolone
- 8 with resistance to cephalosporins and fluoroquinolones
- 4 with resistance to fluoroquinolones or cephalosporins

How widespread is the problem?

We believe this is just the tip of the iceberg. Our research is the equivalent of a pilot study, with more extensive research required to establish the full scale of the problem. Pharmaceutical pollution is an emerging issue and even developed regions, such as Europe, could make considerable improvements to their regulatory framework. The European Commission's Strategic Approach to pharmaceuticals in the environment is already more than a year late, which is concerning.

What can be done?

The Review on Antimicrobial Resistance characterizes pharmaceutical manufacturing pollution as "a supply chain problem that pharmaceutical companies and their suppliers need to solve together" (3). We couldn't agree more. Pharmaceutical companies have a duty to stamp out pollution throughout the supply chain by implementing clean production and appropriate waste management at their own factories and those of their suppliers, integrating environmental criteria in all their contracts, ensuring technology transfer to companies in their supplier base, and ensuring appropriate audits and follow-up actions take place. Regulators must act to include environmental criteria in the Good Manufacturing Practice (GMP) framework, and GMP inspections should be significantly strengthened. In addition, regulators should demand more transparency in the pharmaceutical supply chain.

When it comes to addressing the global AMR challenge, tackling drug resistance due to irresponsible production and opaque supply chains is low-hanging fruit. This is an issue that must be addressed head-on across the board – failure to act will negatively impact the reputation of the industry as a whole.

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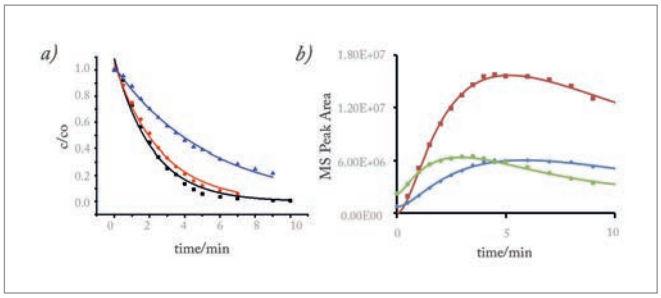

Figure 3. (a) Normalized concentration-time (c-t) curves of azithromycin from UV-irradiation of 20 mM aqueous solutions at pH 3 (black, k = 0.47 min-1), pH 7 (red, k = 0.39 min-1) and pH 9 (blue, k = 0.19 min-1). (b) C-t curves of the photodegradation products of azithromycin at pH 3. The following c-t curves are shown where the numbers indicate the nominal mass: 592 (red), 735 (green), 720 (blue). C-t curves were determined using off-line HPLC-MS analysis. Curves were simulated according to first-order and follow-up and subsequent follow-up chemical kinetics using MatLab.

A sea of data

A major challenge for the identification and quantitation of the pharmaceuticals is the complexity of the matrix of the different waters – coupled with the low concentrations. The large volume of analytical data involved renders interpretation particularly tedious, especially for conventional univariate data analysis. To this purpose, multivariate data analysis techniques have been thoroughly investigated and applied during the last decade (18, 19). Indeed, we rely heavily on multivariate data analysis and chemometrics to analyze the complex data obtained, using MatLab software and its applications, such as the PLS toolbox from Eigenvector Research (see Figure 2).

Multivariate data analysis methods applied in environmental sciences can be divided into two main groups: quantitation using regression methods, and qualification or identification using classification methods. The most common multivariate data analyses for classification purposes are principal component analysis (PCA), factor analysis (FA), cluster analysis (CA) and discriminant analysis (DA). Applications of chemometric methods in wastewater analysis include chemical mapping of antibiotics and identifying sources of entry and retention in the environment (20, 21). For quantification, multivariate linear regression (MLR), partial least squares (PLS), multivariate curve resolution (MCR) and parallel factor analysis (PARAFAC) are often used (18, 22), alone or in combination. The determination of pharmaceutical concentration in surface water was described in a recent illustrative study using PCA and CA (19, 23, 24).

Studying the photo-induced degradation of pharmaceuticals under different conditions resulted in data with complex interdependencies, not only with respect to the kinetic parameters but also to compound descriptors, such as lipophilicity, logP, acidity, pKA, and others. Exemplar PCA results are presented in Figure 2. The left diagram (a) relates classes of antibiotics to their degradation behavior. Plot (b), on the right, relates the reaction conditions to the reaction rates. It quickly becomes obvious that harsher reaction conditions (for example, the presence of oxygen and hydrogen peroxide) foster faster degradation, as expected.

	class	*k/ min-1 0 mg/L H2O2*	*k/ min-1 10 mg/L H2O2*	*k/ min-1 30 mg/L H2O2*
Ciprofloxacin	fluoroquinolone	0.14	0.35	0.44
Enoxacin	fluoroquinolone	0.20	0.31	0.43
Levofloxacin	fluoroquinolone	0.29	0.44	0.43
Lomefloxacin	fluoroquinolone	0.57	0.93	1.03
Norfloxacin	fluoroquinolone	0.25	0.33	0.48
Azithromycin	macrolide	0.47	2.05	1.12
Erythromycin	macrolide	0.10	1.41	1.71
Metoprolol	β-blocker	0.33	0.68	0.98
Sulfamethoxazol	sulfonamide	0.76	1.15	0.84
Sulfamethazin	sulfonamide	0.16	0.19	0.29
Doxycyclin	tetracycline	0.38	0.44	0.76
Tetracyclin	tetracycline	0.40	0.64	0.85
Sulfamethazin	sulfonamide	0.16	0.19	0.29
Doxycyclin	tetracycline	0.38	0.44	0.76
Tetracyclin	tetracycline	0.40	0.64	0.85

Table 1. First-order degradation rate constants, $A \xrightarrow{k_{deg}} B$), [kdeg] = min-1 of selected pharmaceuticals as determined from the HPLC-ESI-MS peak area. The initial compound concentration was 20 mg/L dissolved in Milli-Q-Water at pH 3-4. UV-irradiation was achieved using a low-pressure mercury lamp.

Breaking it down

To eliminate pharmaceuticals from wastewater, a so-called 'fourth purification stage' in wastewater treatment plants has been discussed for several years (25, 26) and the use of advanced oxidation processes (AOPs) and other degradation techniques has been explored. By using AOPs, oxidation of chemical compounds is achieved via a combination of UV irradiation and ozone or hydrogen peroxide (H_2O_2), or through ozone and hydrogen peroxide and catalysts. Whichever method is used, the result is an increased formation of hydroxyl radicals (OH•), which react very rapidly with almost all organic compounds because of their high oxidation potential. Alternatively, titanium dioxide (TiO_2) can be used as a heterogeneous catalyst. Likewise, the photo-Fenton reaction creates a significant amount of hydroxyl radicals (27–31).

The presence of H_2O_2 as an additive is known to be

favorable for the acceleration of degradation (32–34). But when the concentration of H_2O_2 is too high, there is a risk of supersaturation. As shown in Table 1, we found that supersaturation was only observed for levofloxacin, azithromycin and sulfamethoxazole – all other active ingredients studied were degraded more rapidly with increasing concentrations of H_2O_2. Such detailed knowledge about the mechanisms and kinetics of degradation is essential if we are to achieve complete elimination of drugs from wastewaters.

On UV-irradiation of drugs, phototransformation products are formed, which can be just as dangerous in environmental terms as the parent molecules. To predict whether a drug and its phototransformation products are significantly degraded, we must determine the kinetic rate constants. Most publications report first-order kinetics for the degradation of the main pharmaceutical compound (34), but not the chemical kinetics of the photo-induced transformation products. We set out to rectify this omission by determining both the degradation rates and the half-lives of phototransformation products.

Figure 3 (a) shows examples of the c-t curves of azithromycin and their description according to a first-order reaction model. Different pH values lead to different degradation velocities as indicated by the reaction rate constants; for example, azithromycin degraded slower at pH 9 than at pH 3. The c-t curves of three identified phototransformation products are displayed in Figure 3 (b). These curves could result from follow-up (red, green, blue) and subsequent follow-up (red, green, blue) reactions. It's clear that degradation products are still present when most of the drug has been eliminated. Hence, it will be important to understand their environmental toxicity or adverse effects.

All aboard

We need to address the issue from several angles. A chemical or photochemical purification step could be added in wastewater treatment plants, but also at individual sources of effluents, such as hospitals. Purification closer to the source would allow better elimination, since the drugs won't have been diluted through the sewage system. However, economically feasible translation of purification methods into large-scale operations is still a future aspiration. Perhaps most urgently, we need a better understanding of the toxicity of degradation products.

From a more strategic point of view, we must also consider how we might tackle the problem at its source; for example, by using more thoughtful prescription strategies for drugs such as antibiotics in human and veterinary medicine.

Protecting our water system from errant pharmaceuticals represents a significant challenge for science – and analytical chemistry has an essential role to play. Only with a much greater understanding can we decide what steps must be taken and how quickly; to not act is to turn a blind eye to long-term consequences for our home planet.

Melanie Voigt, Anika Gold, Christina Blaesing, Timo Hoelscher and Martin Jaeger are researchers at Niederrhein University of Applied Sciences, Department of Chemistry, Instrumental Analytical Chemistry, Germany.

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Business

Economic drivers
Emerging trends
Business strategies

Joining Forces: Powerful Proteomics

Collaboration between academia and instrument manufacturers not only pushes analytical science forward faster, it's also good for the soul. In our new "Joining Forces" article series, we tell stories of teamwork – from the initiating spark to the ultimate objective. Our first installment delves into an ambitious proteomics project from the University of Cambridge, the Francis Crick Institute, and SCIEX.

With Markus Ralser, Principal Investigator at University of Cambridge and the Francis Crick Institute, and Mark Cafazzo, Director of Global Academic/Omics Business at SCIEX

Tell us about your project…

Markus Ralser: It's a collaboration between my lab, the lab of Kathryn Lilley (Cambridge Centre for Proteomics) and SCIEX. In my lab, we try to understand the interactions between metabolism and gene expression; we want to understand how cells react to changes in their environment and their nutrients, and how they change the breakdown of those nutrients. Kathryn's lab is proteomics-focused – her role in this project is to contribute knowledge about different approaches to measure and identify proteins. SCIEX is the industry partner, developing technology and providing the instruments and technical know-how.

We work specifically with budding yeast, a small fungus that is a very important model organism in the biomedical sciences – easy to cultivate and informative. We have collections with several thousands of systematically generated yeast strains; ultimately, we want to use SCIEX technology and the expertise of both labs to measure changes in the proteome in all of those strains, and so find out how the genes function. Of course, that has to be a collaborative effort, as it requires skills from several disparate disciplines – no individual can solve such big problems alone.

Mark Cafazzo: We're really excited about the work we're doing with the Ralser lab – and pleased that they think our technology is the right tool to get the job done. It's a great example of how we can work together and how public–private partnership advances the science. It's an incredibly ambitious project...

MR: It certainly is! It sounds simple – "measuring 5,000 proteomes" – but it is actually a big endeavor. Even with all the effort and money that has gone into research of biological systems so far, we have only uncovered the tip of the iceberg. Up to now, we have tried to cut the biological system into minimal units and study them one by one, but that isn't working. Imagine you have a car, and you chop it down, with one scientist studying the wheel, another one studying the key and the next one studying the window – it's very hard to get a complete picture. But as -omics sciences develop, we get an increasingly good overview of how the pieces function together as an entire system.

What are the main benefits of collaboration between academia and industry?

MC: Securing government or grant funding is increasingly competitive. Often, our academic customers find value in partnering with someone in industry for these larger projects, so they can show that there is more than a purely academic interest – there is benefit to the industry, a benefit to the field of research that it's addressing, and ultimately a benefit to society.

From our perspective, the value comes from working with labs that are doing cutting-edge work – it's a big part of how analytical tool providers do

business, especially within academia.

The researchers at the University of Cambridge and the Crick Lab are known in the field of proteomics and metabolomics for their high-quality research. Their work will further the science of proteomics and lead to a better understanding of disease, which is a fundamental need in this age of precision medicine. That's why it's important to us to support them, whether that's direct support, collaborative support or the expertise we have with our own application scientists or R&D specialists when it comes to developing software. Collaborations are a great way for industry to stay directly in touch with thought leaders and get valuable feedback to better design products for the future.

MR: When developing a prototype, the engineers who build a mass spec may never use it. Unless you have it up and running and see it working on a daily basis, you can't always know what problems to expect. By collaborating with us, they are not just putting the instrument in the lab, they are developing it alongside us – and that results in better technology.

For us in academia, there's another factor to consider. We have a lot of young students in our labs, postdocs and PhD students; very few of them will find a job in academia. The sooner our students can make contacts with industry, the better the job they can get in a few years' time. It also helps us get things done much more quickly – academia can be so slow. Industry is more money-driven, whereas we are problem-driven. On the other hand, it's sometimes good for them to see that money isn't everything! Both sides can profit considerably.

How did you build the partnership?

MC: It started with a direct relationship. We got to know the scientists, and it became clear that not only were they customers of SCIEX, but they saw value in using our instrumentation and software to address the challenges in their research. We often develop these kinds of relationships over the course of several years. We may eventually partner with someone in academia and use their input to develop a new product, or get their advice on a beta-product, or give them early access to something that hasn't reached the commercial stage yet.

MR: We've actually worked together for quite a few years now – SCIEX has developed a number of technologies that we use to measure how cells behave and change. These are highly experimental instruments, so we get prototypes in the lab and don't know exactly how we will use them. They run a lot of very complicated background software. We spend a lot of time with SCIEX engineers, working out problems that they may not have anticipated.

"It's exciting to work in this setting, between industry and academia, as the worlds collide – it brings you out of your own niche and informs how your work evolves."

What challenges have you encountered?

MR: If you have a collaboration where three labs are working in parallel on the same problem, then of course things develop in different directions. This project is a three-way collaboration but we have a clear and defined goal, and this makes life much easier. We do have technical challenges, of course, and I can't always predict how we

will solve them – but this is the fun of collaboration – gathering knowledge and overcoming problems together.

MC: Our main challenge is that we don't have unlimited resources, so we always have to justify the work we're doing. There is a need for us to capture benefits for SCIEX from a collaboration like this. It can be tangible and specific, such as a co-written peer-reviewed journal article, or the work being used in marketing materials such as application notes or webinars. We also have to balance the number of collaborations we commit to – we can't possibly collaborate with everybody, so we have to be judicious about which opportunities we select. From the collaborator or researcher's side, the timelines they have in mind may not line up with development cycles, when the availability of certain products might be, and so on – but you just have to work together to find the most beneficial combination.

What makes a collaboration effective?

MC: First and foremost, agreement on the goals of the project and the value that both sides of the collaboration can recognize. The other thing is clear team communication. When we work with a collaborator – especially when it's more than one lab and multiple scientists involved – you have to have a good coordinated effort. There has to be scientific leadership on both sides so that everyone can agree on the project milestones, and there has to be a certain amount of project management.

MR: This particular collaboration works well because we have a clear plan. First, we need to cultivate the yeast, then we need to grow, handle and measure, and in parallel develop the algorithms to analyze the data. It's exciting to work in this setting, between industry and academia, as the worlds collide – it brings you out of your own niche and informs how your work evolves.

Solutions

Real analytical problems
Collaborative expertise
Novel applications

Arrested Development

Given ongoing challenges in sample preparation and a lack of novel alternatives, is it time to give liquid-phase microextraction (LPME) a second chance?

By Stig Pedersen-Bjergaard, Astrid Gjelstad, and Knut Einar Rasmussen

The Problem

Complex aqueous samples, such as biological fluids and environmental water samples, are a real challenge for sample preparation. Current methods are marred by poor sample clean-up, dilution of the sample, and use of solvents. The discovery of liquid-phase microextraction (LPME) in the late 1990s offered a welcome alternative – so why hasn't the technology been commercialized?

Background

Liquid-phase microextraction (LPME) is a microextraction technique for sample preparation prior to chromatography, mass spectrometry, and electrophoresis – and it was first presented by our group in 1999 (1). The target analytes are extracted from an aqueous sample through a thin film of organic solvent, which is loaded as a supported liquid membrane (SLM) in the pores of a porous hollow fiber's walls, and end up in an acceptor solution located inside the lumen of the hollow fiber (Figure 1).

Three-phase LPME can be used for extraction of basic and acidic analytes, based on the fact that partition of such substances in and out of organic solvents is strongly pH dependent (Figure 2). Thus, for basic analytes, the sample is made alkaline, and the analytes are effectively extracted into the SLM in their uncharged state, followed by diffusion across the SLM and extraction into the acceptor solution. The acceptor solution is acidic, the analyte molecules become ionized, and they are prevented from re-entering the SLM. For extraction of acidic analytes, the pH-gradient across the SLM is reversed. After extraction, the acceptor solution is collected for the final analytical measurement.

The Solution

Sample preparation based on LPME has several advantages. First, LPME provides a high degree of sample clean-up from complex biological and environmental samples, because the non-polar nature of the SLM prevents most matrix components from entering the acceptor solution. For example, with human plasma samples, matrix components, such as proteins, salts, and phospholipids, are not extracted into the acceptor solution.

Second, LPME can provide high enrichment of analytes, due to the small (typically 5–25 µL) volume of the acceptor solution. From small biological fluid samples of around 250–500 µL, enrichment factors in the range of 10–20 are typically obtained. From large samples of environmental waters, enrichment factors exceeding 25,000 are possible (2).

Third, the acceptor solution is aqueous in the three-phase mode, and is directly compatible with liquid chromatography-mass spectrometry (LC-MS), high-performance liquid chromatography (HPLC), and capillary electrophoresis (CE), with no evaporation and reconstitution required. In two-phase LPME, neutral analytes can also be extracted, and because the acceptor solution is organic, two-phase LPME is directly compatible with capillary gas chromatography (GC).

We carried out the initial proof-of-principle experiments for LPME in 1998, and patented the work together with the university's technology transfer office. We were inspired to a large extent by the development of solid-phase microextraction (SPME) (3) and SLM extraction (4). Personal contacts put us in touch with Varian, Inc (Torrance, CA, USA), who licensed the patent application. We worked with scientists at Varian to develop a prototype 96-well plate system for LPME (Figure 3) – a prototype that was tested in several US pharmaceutical industry laboratories, and performed well. However, Varian

- Extraction into µL liquid volume directly compatible with liquid–phase separations techniques
- No evaporation and reconstitution before chromatography/ electrophoresis
- Compatible with complex biological samples
- Inexpensive and single-use
- No carry-over
- High pre-concentration

Table 1. Why use LPME?

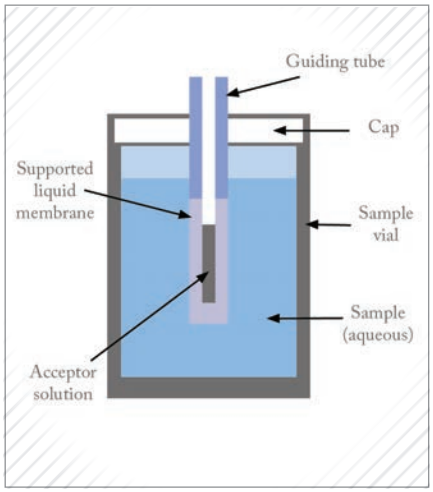


Figure 1. Principle of LPME

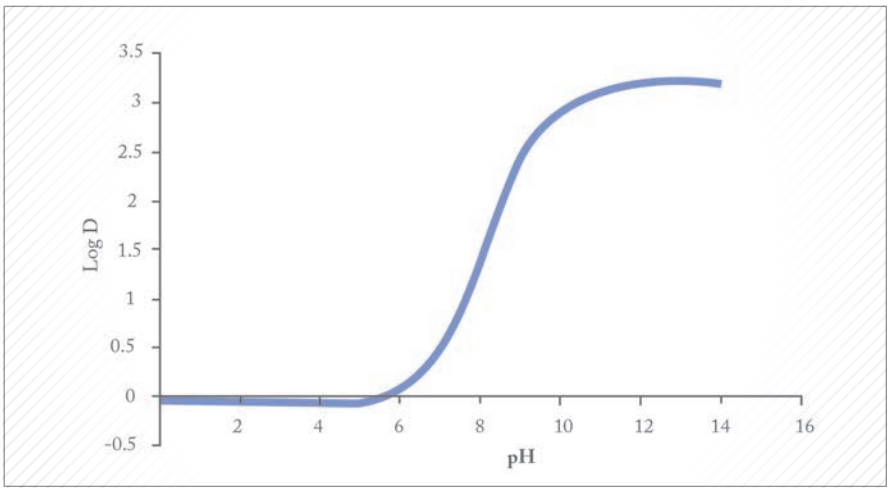


Figure 2. Partition coefficient (log D) for paroxetine between octanol and aqueous solution as function of pH. A high log D indicates strong partition into organic phase.

ultimately decided not to bring the 96-well LPME technology to the market.

The project with Varian was terminated for several reasons, including:

- Poor extraction kinetics due to inappropriate device geometry
- High estimated costs of mass production of the technology
- High estimated costs to develop an application database

Termination of the collaboration was a major disappointment. We later had discussions with a couple of other US-based companies about licensing the technology, but with no success. As university professors, we learned a lot from this industrial collaboration; the industrial mindset is very different from academia, and we now keep the industrial viewpoint in mind during our fundamental research. In particular, the experience has made us much more critical; we now aim for the technology we develop to be highly competitive in terms of workflow, costs, speed, and automation.

Beyond the Solution

Although LPME was invented more than 15 years ago, there is still significant interest in the technique within the scientific community, and around 80 research papers are published every year utilizing LPME. The majority of these papers are related to biomedical, environmental, and food and beverage applications. However, recent trends include the use of electrical fields across the SLM, and different hyphenations with molecular-imprinted polymers and nanoparticle technologies, to mention just a few.

In addition, several papers on automation have recently been published. Automation is mandatory for implementation of LPME in routine laboratories, but there is currently no commercially available equipment to allow this. Therefore, we recently developed a variant of LPME, termed parallel artificial liquid membrane extraction (PALME), which is based on existing 96-well plate technology intended for filtration (5).

We first published our work on PALME in 2013 (5), and filed a patent application in collaboration with the University of Oslo's Technology Transfer Office. The principle of PALME is illustrated in Figure 4. The equipment comprises a 96-well sample plate and a 96-well filter plate. In the bottom of each well in the filter plate, there is a small filter of a porous polymer (100 µm thickness), and this serves as support for the SLM. First, the samples are pipetted into the sample plate. Second, 3–5 µL of organic solvent is pipetted into the filters, and the immobilized solvent serves as the SLM. Third, acceptor solution is pipetted into the reservoirs above the filters in the filter plate. Finally, the sample plate and filter plate are clamped, and agitated for 30–60 mins. During agitation, target analytes are extracted from the sample, into the SLM, and further into the acceptor solution.

Compared to LPME, PALME is restricted to relatively small sample volumes due to the 96-well geometry. The technology fits very well into pharmaceutical and biomedical laboratories, where sample volumes of 10–1000 µL are the norm. In contrast to LPME, PALME can be performed with industrial equipment – all liquid handling can be performed with multi-channel pipettes, and PALME has a high potential for automation. The advantages of LPME are maintained: no evaporation and reconstitution, excellent sample clean-up, moderate analyte enrichment, and only 3-5 µL solvent consumption per sample. The enrichment in PALME is less than in LPME, but sufficient for most pharmaceutical and biomedical application when combined with LC-MS.

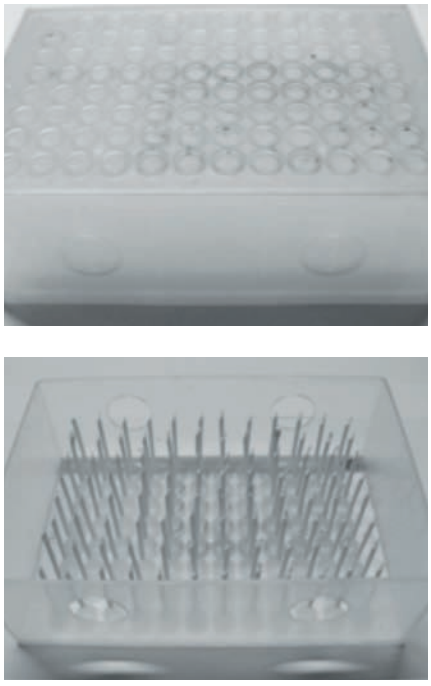
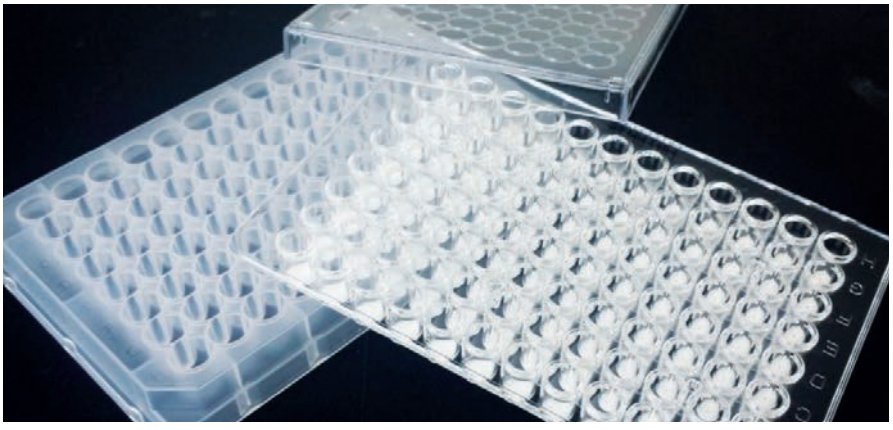


Figure 3. 96-well LPME equipment

To date, our work with PALME has been performed with commercially available 96-well plates (5-8). The filter plate is the most critical part of the PALME equipment, and in our initial work we used filter plates equipped with polyvinylidene fluoride (PVDF) filters. However, this polymer is not ideal and we have observed non-specific binding of target analytes (5).



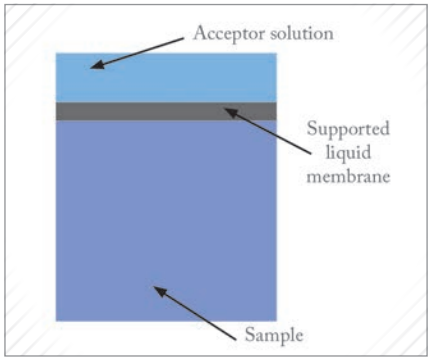


Figure 4. Equipment and principle for PALME.

Non-specific binding can be reduced or circumvented by careful optimization of the chemical composition of the SLM, using mixtures of organic solvents. However, this complicates PALME method development. Therefore, we are developing special 96-well filter plates optimized for PALME, which are not prone to non-specific binding. With this product available in the near future, setting up PALME methods in routine laboratories showuld be feasible.

Like all other methods, PALME has its advantages and its limitations. Based on current knowledge, PALME is ideal for extraction of basic and acidic analytes with a log P > 1 from aqueous samples, and for use in combination with LC-MS (and HPLC and CE). Such applications are common for drug analyses conducted by pharmaceutical companies, hospitals, analytical services contract laboratories, forensic toxicology laboratories, and doping laboratories. For final acceptance and implementation into routine use, the release of a commercial product optimized for PALME is critical (as discussed above). Longer term, development of extraction protocols for more polar analytes will also be an important step forward.

We welcome collaborators who wish to assess PALME – as well as the constructive comments and even criticism that follow. We would also be interested in talking with any industrial partners who would like to consider the potential of commercialization.

We are passionate about bringing the excellent performance and simple workflow of PALME into routine use, and we see our enthusiasm reflected in the eyes of our collaborators.

Stig Pedersen-Bjergaard is a professor in the Department of Pharmaceutical Chemistry, Astrid Gjelstad is an associate professor in the Department of Pharmaceutical Chemistry, and Knut Einar Rasmussen is professor emeritus – all at the University of Oslo, Norway.

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Gadgeteer at Heart

Sitting Down With... Milton Lee, H. Tracy Hall Professor of Chemistry, Department of Chemistry and Biochemistry, Brigham Young University, Provo, Utah, USA.

What drew you to the scientific field?

I've always had a desire to do practical things; at graduate school in Indiana, my interest was in environmental analysis – specifically, polycyclic aromatic hydrocarbons in air pollution, and from tobacco and marijuana smoke. I also like to build things – I'm kind of a 'gadgeteer'. I like to see things mechanically, see electronics put together and become useful. One of the first things I did as a graduate student in Milos Novotny's laboratory was design and build a capillary column injector for the gas chromatographs we were using. I have a tendency to get bored with repetition, and enjoy having more variety – going into the field and lab, writing papers, giving talks. I've always insisted on having my office right next to the laboratory so I have easy access to what my team is doing.

Collaboration seems very important to you...

Early in my career, an established chromatographer advised me that if I wanted to be successful, I shouldn't look for collaborations with other established people, but come up with my own ideas and develop my own group. I thought that was the wrong way to approach it. Maybe that is the way to become famous, but I much prefer working with other people. I'm not interested in being my own little island! Collaboration brings expertise from a wide variety of disciplines and viewpoints – expertise that I don't have. I've worked with mechanical engineers, electrical engineers, chemical engineers, microbiologists, physicists and statisticians. It also brings inspiration and fun – some of these people have become my best friends over the years. I think a lot of my success – and enjoyment – has been due to my associations with other scientists and colleagues, both in the academic and industrial worlds.

What's the secret to successful collaboration?

The key factor is being able to get along with people and work with them effectively – and not being concerned about getting all of the credit for discoveries. Collaborations usually start with a need; first, I'll ask around, see who has the expertise I'm looking for. In most cases, people are excited to get involved in something a little different. People who are in engineering or biology approach problems from different angles than analytical scientists. That's how you get creativity – by building up ideas together. I encourage my students to think the same way.

How important is it to have contact with industry?

It's deeply important. I've had good interactions with all the analytical companies who have produced chromatographic and mass spectrometry instrumentation. Back in the early days, I worked with Hewlett Packard; and more recently I have had great collaborations with companies like Restek, Supelco, PerkinElmer and Valco. Academicians have a lot of freedom to present at meetings and publish papers, but I feel there are industry researchers who are just as creative, but who aren't able to publicize their work. It bothers me that they don't receive the recognition they deserve. When you judge a person's contribution on the number of publications, you're immediately excluding great people in industry who don't have that opportunity.

What has been your most rewarding collaboration?

There are many, but here is one example. When I worked in supercritical fluid chromatography, I was interested in interfacing to mass spectrometry, and one of the other professors had a postdoc working in supersonic jet spectroscopy. We got talking about what a supersonic jet ion beam would do in mass spectrometry, and came up with the idea of doing supersonic expansion of ions and orthogonally pulsing them to get maximum sensitivity. We published the first paper on orthogonal extraction-mass spectrometry where the ions were created at atmospheric pressure – an exciting instrumental project that was very rewarding to me personally.

You're based at a church-sponsored university. How does your religion influence your work?

In the Mormon religion, family and religion go hand in hand, and being a Christian has affected my profession a lot. Some people believe that science and religion don't go together but I look at it this way: in both science and religion, you're seeking the truth. My scientific knowledge has never interfered with my religious beliefs. Among many things, religion teaches principles of honesty, integrity and ethics – and it's important for me to make sure that what we're doing in the laboratory is right, and that we're reporting things as accurately as possible. It's worth noting that most of my students are not Mormons; they come from all around the world and become immersed in the scientific culture of the university.

How would you define scientific success?

I think of success broadly. It can be discovering some fundamentally new phenomenon, but it can also be developing new techniques or tools, or even improving analytical practice and enhancing chemical analysis itself. I think the ultimate success, though, comes from what you do for others and what you leave behind. In my religion, there's a saying: "No success can compensate for failure in the home". My family is my most important 'work' and where I gain the greatest satisfaction. Having said that, my profession, my research and my discoveries have been enriching, exciting and challenging. A good job is one you enjoy, one that allows you to live well – and one that allows you to have a few adventures...

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