4-2015

Analytical Chemistry Research at Primarily Undergraduate Institutions: Training Tomorrow's Investigators [post-print]

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Analytical Methods

RSCPublishing

MINI-REVIEW

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Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

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Primarily undergraduate institutions (PUIs) are a unique training ground for young scientists who work closely with faculty on their research. Researchers at PUIs face a number of challenges, including balancing research and teaching responsibilities, obtaining sufficient funding for projects, and training students in their first research experiences. Faculty at PUIs deploy a variety of strategies to address these challenges, and the resulting research provides important benefits to faculty, students, the analytical chemistry community, and society. This review discusses these challenges and benefits in detail. Additionally, several vignettes describe how specific faculty members have established and maintained productive research programs at PUIs, and select publications since 2009 by PUI researchers are highlighted.

Primarily undergraduate institutions (PUIs) occupy a unique space in American higher education. While these institutions share a common focus on educating undergraduate students, they are a diverse group, ranging from two-year community colleges to four-year public institutions and liberal arts colleges (Figure 1a). PUIs also differ in the presence or absence of Master's programs, which enroll students engaged in full-time research. Over 2000 institutions in the United States can be classified as PUIs, and these institutions enroll 63% of the student population.[1]

Research at PUIs

While teaching is a major component of a PUI professor's daily life, many of these institutions also encourage, support, and expect faculty to maintain an active scholarly life. Research activities raise an institution's profile, which is one reason to encourage faculty participation; however, most PUI research programs also are expected to contribute to undergraduate teaching and training. For faculty members and students, a number of synergies can exist between research and teaching at institutions of all sizes.[2] At PUIs, this connection is particularly strong since laboratory research is necessarily conducted by undergraduates; however, realization of the benefits of undergraduate research at a PUI requires faculty to address a number of challenges, including balancing teaching and research expectations, securing sufficient funding, and training novice students to conduct publishable research.

Teaching expectations vary widely between PUIs, but all PUI faculty must learn to balance teaching and research activities. Faculty at PUIs typically teach from two to five courses per semester, and the enrollment for these courses and the availability of teaching assistants varies between institutions. As a result, research productivity at a PUI may be uneven throughout the year, ramping up in the summer and tapering off in the fall and spring when teaching activity is more intense.[3] Higher levels of productivity during the academic year are supported by incorporation of research into teaching laboratories,[4] maintenance of a well-trained and active undergraduate research group, and regular sabbaticals. Ideally, institutional expectations with respect to research activities are matched by the level of support provided through course release, compensation, and research funding; however, this is not always the case.

Research at PUIs is generally performed, by necessity, at much lower cost than work at research universities. Financial support for research at PUIs is as variable as the institutions themselves with wide ranging levels of start-up funding, infrastructure, and institutional support for grant writing and sabbaticals. Although comprehensive data on start-up packages is difficult to obtain, crowd-sourced data on start-up funding for biologists at M.S.-granting comprehensive universities and liberal arts colleges report packages ranging from \$0 to \$200,000 (median of \$30,000 for 23 institutions).[5] These start-up packages can be supplemented by private and federal funding dedicated to

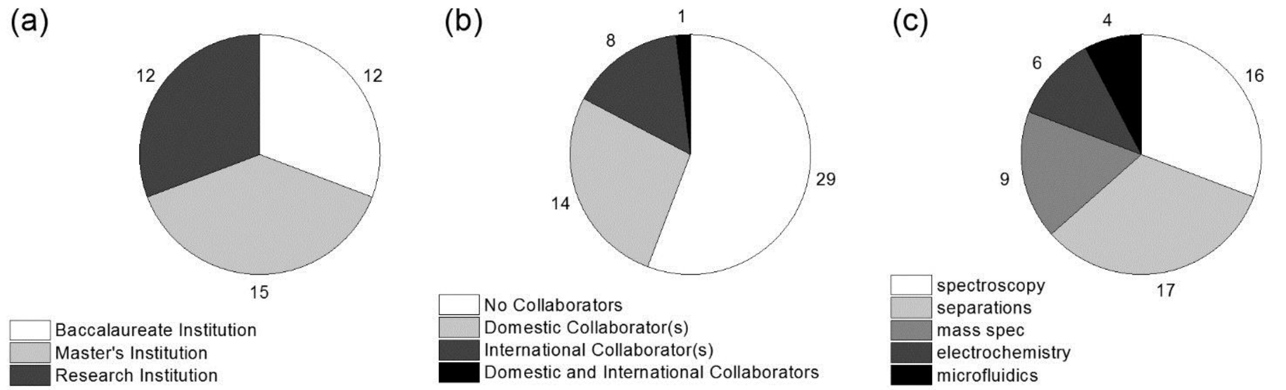

Figure 1. An overview of the research cited in this mini-review, which includes 52 primary articles published by a total of 39 investigators at PUIs. Although the list of references discussed here is far from comprehensive, it should be reasonably representative of recent publications by analytical chemists at PUIs. (a) The representation of cited research groups from Baccalaureate colleges, Master's granting institutions, and research universities, as classified by the Carnegie Foundation for the Advancement of Teaching. Publications from research institutions were included when the institution was AREA-eligible and/or had undergraduate populations that were ≥76% of enrollment. The distribution in (a) does not include the institutions of co-authors from collaborating non-PUI institutions. (b) The fraction of cited publications that were co-authored with collaborators. (c) Cited publications by sub-field.

supporting undergraduate research. For example, Research Corporation and the Dreyfus Foundation both sponsor grant programs specifically to fund research at PUIs. The National Science Foundation (NSF) supports the Research at Undergraduate Institutions (RUI) program, and the National Institutes of Health fund Academic Research Enhancement Awards (AREA) for institutions receiving less than $6 million from NIH annually. However, these programs represent only a small amount of total federal funding for research. Only 0.5% of the 2013 NIH budget was awarded through the R15 mechanism for AREAs, although research productivity for these awards is high, suggesting that they provide good value.[6] The National Science Foundation supports comparably more undergraduate research. Nevertheless, funding for research at PUIs remains a small portion of the overall NSF budget. For example, at the BIO directorate from 2002-2012, just 8% of awards and 5% of funding went to research at PUIs.[1] Consequently, researchers at PUIs use a variety of strategies to be productive within funding constraints, including developing more economical methods or models, performing experiments at national user facilities, or collaborating with researchers at larger institutions (Figure 1b).[7,8]

Successful research mentors also invest significant time in training students and socializing them to scientific norms.[5] At the outset of their research, undergraduate students often have little prior knowledge about their projects. Many students start as sophomore or juniors, although some programs, including the Interdisciplinary Science Program at Trinity College, start students in research during the first year of college. Even when students have had some experience in teaching laboratories, many begin their research not knowing how to use a pipette properly or prepare a buffer, much less troubleshoot instrumentation or evaluate data quality. Successful PUI research advisors often work side-by-side in the laboratory with their students, especially early in the student's training but also to help with particularly challenging or lengthy experiments.[9] Once trained, an undergraduate may have only 3-10 hours per week to dedicate to research during the academic year. As a result, summer research is particularly important for progress at PUIs. During the summers, faculty and students can spend more time on research, often working full-time, and students who have worked full-time over a summer tend to be more productive in subsequent semesters during the academic year. Nevertheless, turn-over is rapid in a PUI environment since students (hopefully) graduate in four years. As a result, faculty at PUIs face a special data management challenge since a single student rarely takes a project to completion. PUI researchers must carefully curate data as students join the lab and graduate, guiding a project through publication over time.[9]

If these challenges are met, undergraduate research experiences produce a number of benefits for students and faculty. Student surveys identify a large number of personal and professional gains in students who participate in undergraduate research projects, particularly when students participate over multiple years and when research mentors treat their students as colleagues by engaging them in lab meetings, literature reviews, and conference presentations.[10–13] These experiences improve the retention of minority students in STEM fields[2,11] and often encourage students from all backgrounds to pursue further study in science. For example, on a per graduate basis, liberal arts colleges produce a disproportionate number of eventual STEM PhDs, an outcome attributed in part to hands-on training in undergraduate research.[14] Having participated in undergraduate research, these students enter their graduate research labs with an appreciation for the challenges and methodologies of science.[11] Indeed, undergraduate research is often a formative experience in a scientist's career, and many eminent scientists cite their undergraduate research as an important factor in their choice to pursue a career in science.[15] Working with undergraduates often also benefits the research mentor. For some faculty, the lower stakes of research at a PUI allow them to take risks and explore new area (funding-permitting) based on student interest.[7] Additionally, because undergraduates engage with faculty from departments across campus during their coursework, they can help forge connections to intra-institutional collaborators.

In addition to these personal benefits to students and faculty, successful undergraduate research also produces public good in the form of knowledge creation. In the latter part of this review, I highlight some of the new knowledge to emerge from recent research activity by faculty at PUIs. While many undergraduates participate in projects at research-intensive institutions with doctoral programs, undergraduate research at PUIs presents unique challenges and opportunities, and I have chosen to focus specifically on publications authored or co-authored by researchers at PUIs, including Baccalaureate, Master's, and research institutions with primarily undergraduate populations (Figure 1a). Some, but not all, of the publications were co-authored with non-PUI collaborators (Figure 1b). In identifying these publications, I searched for work supported by the NSF RUI program, the NIH AREA/R15 program, the Cottrell College Science awards from Research Corp., and the Henry Dreyfus Teacher Scholar awards. I also identified recent recipients of the American Chemical Society's Research at Undergraduate Institutions award and polled colleagues for suggestions. Because research with undergraduates often moves at a slower pace than research in labs staffed by postdocs and graduate students, I have included publications since 2009, rather than from the last three years, as would be typical for a mini-review. Importantly, these searches revealed publications from PUI researchers in diverse sub-fields of analytical chemistry (Figure 1c). Nevertheless, I regret that I am sure to have missed many important contributions from PUI faculty. Although a comprehensive survey of recent analytical research from primarily undergraduate institutions would be a daunting task, I hope that this mini-review will highlight some interesting, recent contributions of PUI faculty to the field of analytical chemistry and to training the next generation of emerging investigators.

Spectroscopy

To stay competitive with research groups staffed with graduate students and postdoctoral scientists, PUI researchers must be excellent lab managers. Because undergraduates have limited windows of time during which they conduct their research, projects at PUIs are often divided up among several students with each student taking responsibility for specific aspects of the work. For example, Elizabeth Harbron's research group at the College of William and Mary recently published a nanoparticle-based FRET method for mercury detection.[16] Harbron's students worked on two different teams to complete this research. One team focused on the mercury-responsive rhodamine spirolactam dye, while the other team worked on the polymer nanoparticles that enhanced sensitivity via light-harvesting. In addition to organizing this division of labor, Harbron also coordinated the transfer of skills between students over time. A senior student in the lab, Courtney Roberts, mastered the challenging dye purification step and trained sophomore Desmarie Sherwood. By the time the group was collecting data for the final experiments, Roberts had graduated, but Sherwood was able to purify additional dye to complete the work.

Several other PUI-based groups have recently published fundamental advances and modelling papers on spectroscopic methods. In particular, several articles integrate experimental results and modelling. For example, a recent publication applied kinetic models to ATR-UV-Vis and NIR measurements of small-batch slurry reactions to elucidate process chemistry,[17] and another group compared experimental results and simulations of fluorescence correlation spectroscopy to provide insight on best practices.[18] In another study, a neural network was used to optimize conditions for a fluorescence-based binding assay.[19] Other recent advances improve data analysis or lower costs. For example, high resolution, coherent, three-dimensional spectroscopic studies of gas phase bromine demonstrated how higher dimensionality methods reduce spectral congestion and aid in accurate peak assignments,[20] and a recently published chemometric method makes multivariate calibration of spectral data less demanding.[21] Another paper demonstrated that a relatively inexpensive circuit could facilitate continuous-wave cavity ring-down spectroscopy (CW-CRDS) measurements.[22]

In addition to these fundamental advances, several publications present a range of applications-driven advances in spectroscopic methods. Recent biomedical applications include a molecular beacon for a cancer biomarker,[23] a surface plasmon resonance method for drug screening,[24] and a dynamic light scattering assay for protein-aptamer binding.[25] Another group compared several spectroscopic methods and surface tension measurements to quantify perfluorocarbon binding to protein[26] and developed a model to interpret data from the preferred fluorescence method.[27] A particularly unique application was the development of an emergency beacon based on atomic emission. Researchers designed a telescope to detect flame-excited emission from cesium, rubidium, and potassium salts at varying levels, allowing them to interpret chemical information encoded in the emission intensities from up to 1 mile away.[28] Two PUI-based groups have made contributions to spectroscopic investigations of chiral molecules, using complexing agents to discriminate between chiral compounds in NMR[29,30] and applying chiroptical spectroscopy of metal-ligand complexes to achieve sensitive, selective mercury detection.[31] Notably, all of the cited papers apply advanced spectroscopic techniques, exposing students to aspects of spectroscopy beyond the simple applications of UV-Vis and IR found in the typical undergraduate curriculum. As a result, these papers engage in on-going discussions in the literature about novel techniques, while also preparing students for further study in graduate research labs.

Separations

To develop new technologies for two-dimensional liquid chromatography (2D-LC), Dwight Stoll's laboratory at Gustavus Adolphus College has repurposed used components into novel instrumentation and forged strategic partnerships with industry, including a local start-up and global leader Agilent Technologies. Stoll also works closely with his undergraduate co-authors, providing them with rigorous, in-depth training so that they can produce high quality data while exploring their scientific interests. The result has been a prolific publication record covering both fundamentals and applications of multidimensional separations; Stoll has co-authored 10 peer-reviewed research publications with 13 undergraduate co-authors since starting his faculty position in 2008. Recent research topics range from furanocoumarin detection in vegetables[32] to the effects of pressure and pH on 2D-LC separations.[33,34]

Analytical chemists at other PUIs are actively developing new materials for chromatographic and electrophoretic methods. Advances in microfabrication, self-assembly, organic synthesis, and materials science have contributed to major advances in separation science. Recent research in this area includes the development of bamboo-husk based sorbents for heavy metals,[35] novel applications for hydride-based stationary phases,[36–38] and preparation of self-assembled lipid bilayers on packed silica beds for sensing and separations applications.[39] Related research has characterized existing materials, for example, by applying the peak parking method to determine obstruction factors for polymer monoliths in capillary electrochromatography (CEC).[40] Characterization of mobile phases, solvents, and buffer additives is also an active area of research. Recent papers have investigated the effects of discontinuous buffer conditions on polyelectrolyte coatings for capillary electrophoresis[41] and used methyl-β-cyclodextran to enhance cholesterol coating of C18 stationary phases.[42] These research projects provide an opportunity for students to delve deeply into separations theory and explore the effects of individual variables on selectivity, efficiency, and resolution.

A number of recent papers also highlight applications-driven research in separation science. Biomedical applications include continued development of high-performance thin-layer chromatography (HPTLC) for pharmaceutical and tissue sample analysis,[43,44] a capillary electrophoresis method to detect hemoglobin polymers in blood for anti-doping tests,[45] and a demonstration that iontophoresis in tissue may include an electroosmotic component.[46] Another novel application of separations from PUIs is a swab-based method for sample acquisition, preparation, and HPLC analysis of small molecules from amphibian skin that allows these compounds to be quantified without sacrificing the animal.[47] For analysis of complex mixtures, such as polyaromatic hydrocarbons in urine, one PUI research group demonstrated the advantages of two-dimensional gas chromatography. The high quality of the separation allowed flame ionization detection in lieu of mass spectrometry.[48]

Mass Spectrometry

Mass spectrometry researchers at PUIs must have access to research-grade mass spectrometers, which are often more expensive to purchase and maintain than spectroscopic, chromatographic or electrochemical instrumentation. At James Madison University, Christine Hughey and her students are conducting fundamental studies of negative-ion electrospray ionization (ESI) on a triple quad instrument acquired through the NSF Major Research Instrumentation (MRI) program. In 2012, Hughey and two undergraduate students published an *Analytical Chemistry* paper that investigated the role of polar protic and aprotic solvents on negative-ion ESI.[49] These results led to an NSF-funded RUI grant to continue their work. Another strategy at PUIs is to engage in collaborative MS research. Five of the nine mass spectrometry research papers discussed in this section involved collaborations with more research-intensive institutions, compared to an overall collaboration rate of 43% for the papers cited in this review. For example, Alexandra Stenson's research group at the University of South Alabama collaborates with the National High Magnetic Field Laboratory in Tallahassee. While the absence of an FT-ICR MS instrument at South Alabama could have been an obstacle, Stenson has come to view it as an opportunity. Students accompany Stenson to the user facility at the national laboratory, where they experience a research-intensive environment and see their projects in relation to the broader field of high resolution MS research. Through this collaboration, Stenson and her colleagues established a chromatographic method to fractionate complex samples to reduce isomeric and isobaric species. This work, published in 2010 in *Analytical Chemistry*, provides a method for using more commonly available MS^n instrumentation to access information about humic materials previously obtained only by high field FT-ICR instruments.[50]

As MS-based methods become more important, especially in "-omics" research, more PUIs are investing in MS instrumentation and training students to use it, and research groups at several PUIs are contributing to fundamental studies and novel applications. One practical advance was the development of an interface for continuous removal of ion pairing reagents from chromatography effluent prior to ESI-MS.[51] Other recent studies explore the field of proteomics. For example, PUI researchers recently published a detailed study of the "proline effect" in peptide fragmentation.[52] Another group used LC-MS-MS with isobaric tags to measure metabolic changes in diabetic mice,[53]and a third group developed data acquisition and processing methods to interpret MALDI data into quantitative measures of the phosphoproteome.[54] For small molecule applications at PUIs, DESI-MS and DESI-MS-MS have been used for detection of designer drugs, pharmaceuticals, personal care products, and cosmetics.[55–57] The instrument used for designer drug detection included a miniaturized mass analyzer for increased portability. The combination of ambient ionization, increased portability, and reduced vacuum requirements makes this technology more accessible to law enforcement or emergency medical teams, but also suggests a future where MS technology is more readily available in undergraduate teaching and research labs.

Electrochemistry

Paul Flowers at the University of North Carolina-Pembroke has 26 years of experience training students in chemistry through undergraduate research. Two recent publications from his laboratory highlight creative ways that PUI researchers keep their work moving forward while also contributing to undergraduate education. Flowers co-authored a 2010 *Spectroscopy Letters* publication with undergraduate Jordan Strickland. Strickland started working with Flowers as a freshman, through the NIH-funded Research Initiative for Scientific Enhancement (RISE) Program. After an initial change of project to better match Strickland's research interests, the pair developed a microscale spectro-electrochemical cell with potential clinical applications.[58] In 2011 and 2012, Flowers worked with students in his instrumental analysis class, who complete 4-week independent research projects as part of the laboratory course, to refine the design and methodology. Their preliminary results were developed further by Flowers and student David Blake during a 10-week full-time summer appointment. This work resulted in a fully-characterized spectroelectrochemical cell, constructed from readily available materials and capable of measuring just 20 nL of sample, as described in a 2013 *Analytical Chemistry* paper.[59]

Like Flowers, other PUI researchers are contributing to advances in reagents and technology for electrochemical studies. Novel reagents for electrochemical detection include a ferriprotoporphyrin-based electrocatalyst for H_2S detection *in vivo*[60] and a ferrocene-labeled RNA sequence for competitive binding assays for microRNA.[61] Technological advances in electrochemical detection have been buoyed by progress in nanofabrication and thin films. One group fabricated and characterized gold nanopillar array electrodes with a variety of coatings for sensitive, selective electrochemical detection on-chip,[62] while another advanced applications of DNA hybridization-based sensing by characterizing the stability of DNA on gold surfaces as a function of their conformation and surface interaction.[63] Other technological advances have resulted in novel electrochemical instrumentation or methods. For example, recent research combines fast scan cyclic voltammetry and ac scanning electrochemical microscopy to make topological and chemical measurements of respiration in living cell culture.[64]

Microfluidics

Although microfluidics and miniaturized analysis are relatively new research areas compared to traditional analytical methods, many PUI research groups have gotten involved in the field. As a new faculty member at Trinity College, I am currently adapting ideas from my graduate and postdoctoral research in nano- and microscale electrophoresis to the undergraduate environment. As in other areas of analytical chemistry, many of the challenges posed by microfluidics research at a PUI are also opportunities. Few microfluidic systems are commercialized, and as a result, microfluidics are rarely part of a standard undergraduate curriculum. This means that I have spent much of my first year at Trinity constructing custom equipment and orienting my research students to unique phenomena at the microscale. For my students, this means hands-on experience in soldering, optical alignment, and device characterization, during which they encounter scientific principles from analytical chemistry and engineering. Additionally, the potential for miniaturized analysis devices to be "better, faster, or cheaper" than traditional instrumentation suggest a good fit with undergraduate research schedules and PUI resources.

Inexpensive, rapid prototyping using poly(dimethylsiloxane) (PDMS) makes this material popular for microfluidics research both at PUIs and research intensive institutions; however, its hydrophobicity is problematic for many applications. As a result, substantial research has been directed at improving or tailoring the surface chemistry of PDMS devices. Recent research has included optimization of plasma treatment of PDMS to minimize its oxygen permeability for myosin motility assays[65] and use of a corona discharge to selectively render channels hydrophilic for continuous detection of analytes from segmented droplets.[66] Another challenge for microfluidic devices is the incorporation of a detection system with the fluidic channels. While many sample preparation and separation steps have been miniaturized and automated, detection systems are often macro-scale and custom-built. Two recent publications from PUIs help to address these shortfalls through on-chip electrochemiluminescence detection at micromolded carbon electrodes[67] and design of a microfluidic ELISA for West Nile virus antibodies that interfaces with a commercial plate reader for detection.[68]

Conclusions

Primarily undergraduate institutions occupy a unique space in the higher education landscape, and their contributions to scientific research and training are easily overlooked because they may occur on a smaller scale or over longer time periods. Nevertheless, researchers and students at PUIs are making contributions to every area of analytical chemistry, including resource-intensive areas such as mass spectrometry and newer fields like microfluidics. By highlighting the important scientific results and mentoring that occur at PUIs, I hope that this review will enlarge the audience for publications from

PUIs and encourage investigators at all institutions to engage undergraduates in their research.

Acknowledgements

The author thanks Paul Flowers, Elizabeth Harbron, Christine Hughey, Sandra Stenson, and Dwight Stoll for sharing their experiences conducting research at PUIs and Cheyenne Brindle Elizabeth Casserly, Jennifer van Sickle and Tom Wenzel for helpful comments on this work. This work was supported by Trinity College.

Notes and references

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1 R. D. Slocum and J. D. Scholl, *CUR Q.*, 2013, **34**, 31–40.
2 M. J. Prince, R. M. Felder and R. Brent, *J. Eng. Educ.*, 2007, **96**, 283–294.
3 R. Finn, *The Scientist*, 1997, **11**, http://www.the–scientist.com/?articles.view/articleNo/18664/title/Scientists–At–Four–Year–Colleges–Strive–For–Research–Quality/.
4 T. W. Chapp and M. A. Benvenuto, *Developing and maintaining a successful undergraduate research program*, American Chemical Society, Washington, DC, 2013.
5 Academic Jobs Wiki, http://academicjobs.wikia.com/wiki/Biology_Negotiations, (accessed August 2014).
6 J. Greenberg, *NIGMS Feedback Loop Blog*, 2014, http://loop.nigms.nih.gov/2014/05/a-look-at-our-area-grants/, (accessed August 2014).
7 L. Marsa, *The Scientist*, 1992, **6**, http://www.the–scientist.com/?articles.view/articleNo/12583/title/Doing–Science–Off–The–Beaten–Path–At–Liberal–Arts–Schools/.
8 J. de Paula and J. Stevens, *Generating New Research Ideas*, Bates College, Lewiston, ME, 2003, http://www.bates.edu/Prebuilt/chem-ideas.pdf, (accessed August 2014).
9 D. J. R. Brook, in *Developing and maintaining a successful undergraduate research program*, eds. T. W. Chapp and M. A. Benvenuto, American Chemical Society, Washington, DC, 2013, pp. 51–59.
10 S. H. Russell, M. P. Hancock and J. McCullough, *Science*, 2007, **316**, 548–549.
11 D. Lopatto, *Science in solution: The impact of undergraduate research on student learning*, Research Corporation for Science Advancement, Tucson, AZ, 2009.
12 T. J. Wenzel, C. K. Larive and K. A. Frederick, *J. Chem. Educ.*, 2012, **89**, 7–9.
13 M. C. Linn, E. Palmer, A. Baranger, E. Gerard and E. Stone, *Science*, 2015, **347**, 1261757.
14 T. R. Cech, *Daedalus*, 1999, **128**, 195–216.
15 A. Roe, *Sci. Am.*, 1952, **187**, 21–25.
16 E. S. Childress, C. A. Roberts, D. Y. Sherwood, C. L. M. LeGuyader and E. J. Harbron, *Anal. Chem.*, 2012, **84**, 1235–1239.
17 C. H. Hsieh, J. Billeter, M. E. P. McNally, R. M. Hoffman and P. J. Gemperline, *Anal. Chem.*, 2013, **85**, 5367–5375.
18 J. D. Lam, M. J. Culbertson, N. P. Skinner, Z. J. Barton and D. L. Burden, *Anal. Chem.*, 2011, **83**, 5268–5274.
19 J. Alvarado, G. Hanrahan, H. T. H. Nguyen and F. A. Gomez, *Electrophoresis*, 2012, **33**, 2711–2717.
20 P. C. Chen, T. A. Wells and B. R. Strangfeld, *J. Phys. Chem. A*, 2013, **117**, 5981–5986.
21 J. Ottaway, J. A. Farrell and J. H. Kalivas, *Anal. Chem.*, 2013, **85**, 1509–1516.
22 A. Rasheed and D. B. Curtis, *Rev. Sci. Instrum.*, 2013, **84**, 066109.
23 E. Guetschow, W. Black, C. Walsh and J. Furchak, *Anal. Bioanal. Chem.*, 2012, **404**, 399–406.
24 X. Yi, Y. Hao, N. Xia, J. Wang, M. Quintero, D. Li and F. Zhou, *Anal. Chem.*, 2013, **85**, 3660–3666.
25 V. S. R. Aaryasomayajula, T. Severs, K. Ghosh, R. DeLong, X. Zhang, S. Talapatra and A. K. Wanekaya, *J. Nanomedicine Nanotechnol.*, 2014, **5**, 1000210.
26 L. A. MacManus-Spencer, M. L. Tse, P. C. Hebert, H. N. Bischel and R. G. Luthy, *Anal. Chem.*, 2010, **82**, 974–981.
27 P. C. Hebert and L. A. MacManus-Spencer, *Anal. Chem.*, 2010, **82**, 6463–6471.
28 C. N. LaFratta, I. Pelse, J. L. Falla, Y. Liu, M. A. Palacios, M. Manesse, G. M. Whitesides and D. R. Walt, *Anal. Chem.*, 2013, **85**, 8933–8936.
29 R. L. Clark, B. T. Wenzel and T. J. Wenzel, *Tetrahedron Asymmetry*, 2013, **24**, 297–304.
30 J. A. Howard, M. Nonn, F. Fulop and T. J. Wenzel, *Chirality*, 2013, **25**, 48–53.
31 P. Carney, S. Lopez, A. Mickley, K. Grinberg, W. Zhang and Z. Dai, *Chirality*, 2011, **23**, 916–920.
32 E. D. Larson, S. R. Groskreutz, D. C. Harmes, I. C. Gibbs-Hall, S. P. Trudo, R. C. Allen, S. C. Rutan and D. R. Stoll, *Anal. Bioanal. Chem.*, 2013, **405**, 4639–4653.
33 E. S. Talus, K. E. Witt and D. R. Stoll, *J. Chromatogr. A*, 2015, **1378**, 50–57.
34 D. R. Stoll, K. O'Neill and D. C. Harmes, *J. Chromatogr. A*, 2015, **1383**, 25–34.
35 H. B. Asberry, C.-Y. Kuo, C.-H. Gung, E. D. Conte and S.-Y. Suen, *Microchem. J.*, 2014, **113**, 59–63.
36 A. Dang, J. J. Pesek and M. T. Matyska, *Food Chem.*, 2013, **141**, 4226–4230.
37 J. J. Pesek, M. T. Matyska and A. M. Kim, *J. Sep. Sci.*, 2013, **36**, 2760–2766.
38 C. Kulsing, Y. Yang, C. Munera, C. Tse, M. T. Matyska, J. J. Pesek, R. I. Boysen and M. T. W. Hearn, *Anal. Chim. Acta*, 2014, **817**, 48–60.
39 E. E. Ross, S.-W. Mok and S. R. Bugni, *Langmuir*, 2011, **27**, 8634–8644.
40 G. J. Anderson, Z. LaPier, M. B. Cammarata, T. S. Cullum and M. M. Bushey, *Electrophoresis*, 2010, **31**, 1583–1585.
41 K. E. Swords, P. B. Bartline, K. M. Roguski, S. A. Bashaw and K. A. Frederick, *J. Sep. Sci.*, 2011, **34**, 2427–2432.
42 S. A. Charlton and J. W. Coym, *J. Chromatogr. A*, 2012, **1266**, 69–75.

43 M. Nguyen and J. Sherma, *J. Liq. Chromatogr. Relat. Technol.*, 2014, **37**, 2956–2970.

44 C. O'Sullivan, N. Popovic, B. Fried and J. Sherma, *Jpc-J. Planar Chromatogr.-Mod. Tlc*, 2012, **25**, 259–261.

45 C. R. Harrison and S. Vydha, *Electrophoresis*, 2012, **33**, 1087–1094.

46 Y. Guy, A. H. Faraji, C. A. Gavigan, T. G. Strein and S. G. Weber, *Anal. Chem.*, 2012, **84**, 2179–2187.

47 T. P. Umile, P. J. McLaughlin, K. R. Johnson, S. Honarvar, A. L. Blackman, E. A. Burzynski, R. W. Davis, T. L. Teotonio, G. W. Hearn, C. A. Hughey, A. F. Lagalante and K. P. C. Minbiole, *Anal. Methods*, 2014, **6**, 3277–3284.

48 L. C. A. Amorim, J.-M. Dimandja and Z. de L. Cardeal, *J. Chromatogr. A*, 2009, **1216**, 2900–2904.

49 B. A. Huffman, M. L. Poltash and C. A. Hughey, *Anal. Chem.*, 2012, **84**, 9942–9950.

50 E. N. Capley, J. D. Tipton, A. G. Marshall and A. C. Stenson, *Anal. Chem.*, 2010, **82**, 8194–8202.

51 S. Shi, B. Zhao, G. Yagnik and F. Zhou, *Anal. Chem.*, 2013, **85**, 6598–6602.

52 M. D. M. Raulfs, L. Breci, M. Bernier, O. M. Hamdy, A. Janiga, V. Wysocki and J. C. Poutsma, *J. Am. Soc. Mass Spectrom.*, 2014, **25**, 1705–1715.

53 L. A. Filla, W. Yuan, E. L. Feldman, S. Li and J. L. Edwards, *J. Proteome Res.*, 2014, **13**, 6121–6134.

54 H.-P. Ho, P. Rathod, M. Louis, C. K. Tada, S. Rahaman, K. J. Mark, J. Leng, D. Dana, S. Kumar, M. Lichterfeld and E. J. Chang, *Rapid Commun. Mass Spectrom.*, 2014, **28**, 2681–2689.

55 I. S. Campbell, A. T. Ton and C. C. Mulligan, *J. Am. Soc. Mass Spectrom.*, 2011, **22**, 1285–1293.

56 K. E. Vircks and C. C. Mulligan, *Rapid Commun. Mass Spectrom.*, 2012, **26**, 2665–2672.

57 J. L. Nizzia, A. E. O'Leary, A. T. Ton and C. C. Mulligan, *Anal. Methods*, 2013, **5**, 394.

58 P. A. Flowers and J. C. Strickland, *Spectrosc. Lett.*, 2010, **43**, 528–533.

59 P. A. Flowers and D. A. Blake, *Anal. Chem.*, 2013, **85**, 3059–3063.

60 J. A. Bennett, C. D. Wheeler, K. L. Sterling and A. M. Chiodo, *Electrochimica Acta*, 2013, **88**, 86–93.

61 J. Wang, X. Yi, H. Tang, H. Han, M. Wu and F. Zhou, *Anal. Chem.*, 2012, **84**, 6400–6406.

62 A. Selimovic and R. S. Martin, *Electrophoresis*, 2013, **34**, 2092–2100.

63 S. M. Schreiner, A. L. Hatch, D. F. Shudy, D. R. Howard, C. Howell, J. Zhao, P. Koelsch, M. Zharnikov, D. Y. Petrovykh and A. Opdahl, *Anal. Chem.*, 2011, **83**, 4288–4295.

64 J. A. Koch, M. B. Baur, E. L. Woodall and J. E. Baur, *Anal. Chem.*, 2012, 9537–9543.

65 R. M. Lycans, C. B. Higgins, M. S. Tanner, E. R. Blough and B. S. Day, *Colloids Surf. B Biointerfaces*, 2014, **116**, 687–694.

66 L. A. Filla, D. C. Kirkpatrick and R. S. Martin, *Anal. Chem.*, 2011, **83**, 5996–6003.

67 S. J. Fredrick and E. M. Gross, *Bioanalysis*, 2009, **1**, 31–36.

68 J. Pena, S. J. McAllister and D. Dutta, *Biomed. Microdevices*, 2014, **16**, 737–743.