Journal of Chromatography B, 871 (2008) 141–142

Contents lists available at ScienceDirect

Journal of Chromatography B

journal homepage: www.elsevier.com/locate/chromb

Editorial

Hyphenated techniques for global metabolite profiling

This issue of The Journal of Chromatography B is devoted to the use of hyphenated chromatographic and electrophoretic separations as currently employed for "Global Metabolite Profiling" in metabonomic, metabolomic (including so-called "targeted" metabolomics) and lipidomic studies. Metabolomics seeks to determine the whole complement of low molecular mass compounds present in a sample [1] whilst the related area of metabonomics is defined as the "the quantitative measurement of the dynamic multiparametric response of a living system to pathophysiological stimuli or genetic modification" [2,3] and lipidomics is, as the name suggests, concerned with mapping the extraordinary diversity of the lipid component of biological systems [4]. Achieving these ends requires analytical approaches that can be used to determine the very wide range of metabolites that are encountered in typical biological samples (including neutral compounds, acids, bases and amphoteric substances) over a wide range of polarity and concentrations. There is therefore, an overriding need for robust and sensitive analytical methods that can produce the required comprehensive global metabolite profiles from complex biological samples. The ideal technique for this sort of research would allow analysis to be undertaken directly on the sample in the absence of a need for sample preparation, be capable of high throughput, and be unbiased with respect to the class of metabolites detected. Such methods should be sensitive, robust, repeatable, reproducible, should have a wide dynamic range and be capable of identifying all of the components detected. Indeed the identification of the unknown components in real life samples still remains a major issue. In addition, at the time of the preparation of this special issue, research to define the metabolic composition of different biological specimens remains a "work in progress". Thus, the number of metabolites to be determined in each specimen depends both on its source and on the analytical methodology applied and, at the moment, there is no real consensus on whether to expect 300, 3000 or 30,000 metabolites in a sample of, e.g., rat urine. The manuscripts presented here represent the current state of the art for global metabolite profiling using separation-based methodologies (gas and liquid chromatography (GC, LC) and capillary electrophoresis (CE)) hyphenated to Mass Spectrometry (MS) as a means of detection and identification. These reports show the huge progress that has been made towards the ambitious goals highlighted above. Certainly great advances have been seen with e.g., LC–MS-based approaches to metabolic profiling in the last 5 years, and there seems to be no slackening in the pace of innovation. However, the unbiased analyst will rapidly realise that there remains some distance to go before a technique (or combination of techniques) is found that can do all that is required to provide robust and comprehensive profiles. The scope of this issue is to illustrate the important and rapid developments in the analytical technologies and computing power, and the significant progress that has been made towards the ideal. The special issue also provides discussion of problems, limitations and perspectives in the field *via* both review and research articles.

So, for example one article provides a critical review of the strategies and obstacles in the process from the treatment of raw mass spectrometry signal to component identification. There is also a report on the profile of human cerebrospinal fluid that uses a comprehensive analysis based on LC-MS, GC-MS and NMR analytical platforms.

In another target area described in this special issue the profiling of lipid species (lipidomics) is described. Lipidomics has developed into a major line of research in metabolic profiling, especially with regard to the increased incidence of obesity in the population. Other articles describe some of the novel separation and instrumentation approaches that are still being developed such as, e.g., high temperature liquid chromatography and ion mobility spectrometry. There is a significant trend towards the application of the highest efficiency separation methodologies (such as ultra performance liquid chromatography) combined with the most advanced mass spectrometric tools such as the new Time of Flight and Orbitrap instruments. The numerous combinations available may, in the short term, in fact represent an obstacle to the consolidation of the field as comparison of results from different laboratories, and method transfer, may not be possible if different instrumental configurations are used. A way forward for GC–MS may be the production of libraries of retention indices that could be of shared use between researchers.

The bulk of the articles contained in this issue describe non-targeted analytical approaches for metabolite profiling, combined with advanced chemometric techniques for data treatment and biomarker discovery. However, along with these untargeted methodologies the issue also contains a number of "targeted metabolomics" applications with reports focusing specifically on, e.g., steroid or bile acid profiling.

As will be clear from reading the articles contained in this volume it is now realistic to claim that the application of advanced, information rich, spectroscopic techniques, hyphenated to separation systems, represents an essential component of the systems biologists' "toolkit" when it comes to the generation of global metabolic profiles of the type required for

1570-0232/$ – see front matter
doi:10.1016/j.jchromb.2008.07.003

metabonomic/metabolomic/lipidomic studies. Certainly this type of profiling represents an important and growing area of bioanalysis. Each of the techniques described has advantages and limitations and their use, and the subsequent interpretation of data generated by them, all require care. Global metabolite profiling is a dynamic and rapidly evolving area and many challenges remain. Not the least of these is in the area of ensuring data quality, and as these separation-based methods have moved out of the initial exploratory phase and into more and more applications, "validation" has become an increasing issue. This is a real challenge, after all how do you develop a method for hundreds, possibly thousands, of analytes present in a sample when you do not know their identities at the start of the analysis, and may not have standards for them at the end (assuming that you can identify them in the first place)? The analytical technology may not be mature yet, but it is not unreasonable to anticipate that significant developments will occur in data extraction, feature detection, statistical analysis and marker identification. The multidimensional data generated by hyphenated technologies in this type of "holistic" metabolite analysis, contains a wealth of information along with an enormous background of chemical, biological and electronic noise. Extracting the useful information from complex datasets represents a major bottleneck for the further development and application of these assays for academia, industry and the regulators. Examining and comprehending the data is much more time consuming and effort demanding than generating it in the first place [5]. It may require chromatographers to forfeit the classical perception of a Gaussian peak, in order to understand the way such informatics tools operate. Strong potential is seen in the evaluation and improvement of the existing and the development of new data extraction algorithms, the combination of the various statistical approaches, and the correlation of data from different omics fields, for example the combination of genomic, proteomic, metabonomic/metabolomic and clinical data in systems biology studies.

The articles and reviews collected here provide a snapshot of the current separation-based methods used for generating global metabolite profiles and as such reveal the relative strengths and weaknesses of the individual technologies. The editors hope that this collection of information will prove to be of interest both to those already engaged in the production of global metabolite profiles and also to those wishing to learn more about the field in general. We would like to thank the authors and the reviewers for their efforts and important contribution in the realisation of this special issue. Also we would like to thank Dimitrios Tsikas for his support and cooperation though the editing process.

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Guest Editor
Georgios Theodoridis*
Guest Editor
Ian D. Wilson

Aristotle University of Thessaloniki, Laboratory of Analytical Chemistry, Department of Chemistry, 54006 Thessaloniki, Greece

* Corresponding author. Tel.: +30 2310 997718; fax: +30 2310 997719.
E-mail address: gtheodor@chem.auth.gr (G. Theodoridis)

Available online 10 July 2008