Preface

Dear Reader,

With this book we want to illustrate how two quickly growing fields of instrumentation and technology, both applied to life sciences, mass spectrometry and microfluidics (or microfabrication) naturally came to meet at the end of the last century and how this marriage impacts on several types of applications.

Since the mid-20th century, the techniques of mass spectrometry (MS) have seen tremendous growth for both biochemical detection and analysis purposes. In particular, new developments regarding MS techniques have been strongly driven by the explosive expansion in the field of biological sciences since the elucidation of the structure of DNA by Watson and Crick in 1953. Quickly thereafter, the quest for understanding biological paths and processes and the need for characterizing an increasing amount of new and unidentified biological species resulted in a demand for new and powerful analytical techniques and tools. MS quickly turned out to be one key technique to perform such studies and research on biomolecules. MS capability became broadened with more recent technological developments such as (i) the discovery of two soft ionization techniques facilitating the analysis of large (bio)molecules and (ii) MS coupling to a liquid-based separation for analysis of more complex samples. In parallel, the capability of MS techniques has been enhanced and has evolved so as to be suitable for handling small volumes of samples down to the low microlitre range. These different evolutions turned MS into a mature technique for the analysis of a wide range of compounds and that of small and complex biological samples. The growth of MS techniques is still best illustrated by the current large interest in proteomics, for which MS is by far the most preferred analytical technique.

Later in the 20th century, biology also impacted on the field of analytical chemistry, especially for biological, medical and diagnostic purposes. The rapid expansion of this field resulted in a need for fast, integrated, portable, more reliable and more sensitive tools that could handle reduced-size samples. This

Miniaturization and Mass Spectrometry
Edited by Séverine Le Gac and Albert van den Berg

Published by the Royal Society of Chemistry, www.rsc.org

gave rise to a new trend in miniaturization for a number of applications and the increasing use of microfabrication techniques to produce micrometer-sized devices for chemical processing, analytical chemistry, biological analysis and diagnostic purposes. However, a new challenge quickly arose from this extreme miniaturization: the detection of the analytes and compounds of interest. Analysts decided to have recourse to MS as a consequence of the strong potential of this detection and analysis technique, together with its suitability to work on low-concentration and reduced-size samples. Additionally, MS was already prevailing for proteomic analysis, and the first microfluidics-to-MS connection was reported for on-line analysis of protein samples processed on a microfluidic device.

The use of MS in combination with microfabricated devices extended to other fields of application, not only biological and medical analysis, but also organic chemistry and the study of organic reactions with their on-line analysis at the outlet of a microfluidic system. For the latter application, this microfluidic-MS hyphenated technique exhibits novel performances and provides a new insight in to reactions compared to conventional tools in organic chemistry.

Other sectors have been reached since then by the combined use of microfabrication and MS techniques, such as forensics and homeland safety. For instance, microfabrication techniques are now also used in view of the miniaturization of the mass spectrometer itself and its implementation on a microchip to "kill" the current paradox of combining tiny devices for sample preparation to bulky and almost room-sized instrumentation. From such ongoing development, one can expect soon the appearance of fully integrated and portable devices for on-site analysis, with both the implementation of the microfluidic-based sample preparation step and the MS analysis on a single device of a few inches in size.

In spite of this "matching" marriage between miniaturization and MS and the fruitful ongoing research into various applications using this unique combination, no book has yet aimed at highlighting the potentials and benefits of this hyphenated tool. Until now, only a number of reviews have focused on one particular subfield of application without giving a really comprehensive coverage of this field of "miniaturization and mass spectrometry" or describing the real status of the field. With this book we hope to give to the reader a better and complete overview of this combined field and to convince people who are new in the field of the potential and the capability of allying mass spectrometry to the trend in miniaturizing chemical processing and analytical tools.

The book covers several subtopics of miniaturization and mass spectrometry. It combines (i) technological developments in the quest for miniaturization of sample preparation and how to connect micrometer-sized devices to a mass spectrometer, (ii) various illustrations of fields that benefit from such a hyphenated technique and (iii) technological developments for the miniaturization of the mass spectrometer. Additionally, the book is not restricted to one ionization technique as is often the case for many reviews, but it reports on efforts for both the ESI and MALDI ionization techniques. After an introduction to miniaturization and mass spectrometry, the book is divided in three sections that respectively concern (i) ESI-MS applications, (ii) MALDI-MS applications and in every section both the connection of a micrometer-size system to MS and applications of this coupling are illustrated and (iii) the miniaturization of the mass spectrometer.

The first chapter gives a comprehensive introduction to the combination of miniaturization and mass spectrometry by approaching several aspects of this coupling. After a short recall of MS analysis and of the two soft ionization techniques of ESI and MALDI, we mention a number of motivations that encouraged people to use microfabrication techniques in the field of MS analysis and we describe also how they have done it and for which fields this unique combination is applied.

The first section of the book focuses on ESI-MS techniques and reports on various strategies to connect a microfluidic or microfabricated device to ESI-MS and on some applications of such a microfluidics-to-ESI-MS coupling. Early coupling strategy between a microfluidic system and ESI-MS using a conventional ionization source and a transfer capillary is described by Daniel Figeys. The following chapters review microfabricated approaches for ESI-MS coupling with ionization sources integrated or not (yet) on a microfluidic system and using various materials, silicon as well as different types of polymers. Gary Schultz presents a conventional silicon and dry-etching-based approach to produce ESI Chip™ that includes 100 individual capillary-shape ionization sources that are operated by a robotic interface making the link from a 96-well plate to an ESI Chip™. Polydimethylsiloxane (PDMS), which is one of the most popular materials nowadays for microfluidics applications, has also been used to produce nanoESI sources, and Kim and Knapp describe here the production of PDMS-based nanoESI sources using three different machining routes as well as their testing. An original design for nanoESI tips that resembles the shape and the functioning of a fountain pen is reported by Le Gac *et al.* through several generations of prototypes either based on SU-8, a photopatternable resist, or polysilicon so as to achieve smaller dimensions and enhanced ionization performance. The last nanoESI microsystem described by Yang *et al.* is made from cyclo-olefin polymer and includes a parylene-based nanoESI interface. The performance of multiplexed devices comprising of a two- or a four-channel tip array is demonstrated, notably for bioanalysis applications and the detection of a small drug in crude urine samples.

The ESI section continues with three contributions on the application of microfluidics and ESI-MS coupling for proteomic analysis or on-line chemical investigation. Iulia Lazar gives a first example of a fully integrated glass-based microfluidic system applied for biomarker discovery and proteomic analysis; the system presents both horizontal and vertical integration and is comprised of six independent devices each including an electroosmotic flow-based pump, a liquid chromatography separation system with a pre-injection/concentration step and an inserted nanoESI capillary source. A second illustration in the field of proteomics is provided by Ghitun *et al.* with a polymer-based microfluidic platform for multidimensional chromatography and on-line nanoESI-MS analysis using an integrated nanoESI source: they especially illustrate the capability of their integrated platform combining ion exchange and reverse phase chromatography for the identification of low-abundance species starting from crude cellular extracts. The last application of a microfluidics-and-ESI-MS combination focuses on chemical investigations. For that purpose, Brivio *et al.* describe and discuss two alternative approaches for coupling a microfluidic system to nanoESI analysis, with or without the use of an ionization capillary source and they notably illustrate the performance of their systems for on-line monitoring of both supramolecular interactions and organic reactions.

The MALDI-MS section is comprised of three chapters, reporting on different aspects of the combination of microfluidics and MALDI-MS analysis. In the first chapter, Musyimi *et al.* discuss the pros and cons of off-line *vs.* on-line analysis using microfluidics and MALDI-MS and particularly describe a very original interface based on a rotating ball to couple a microfluidic sample preparation step to an on-line analysis using MALDI-MS. Thereafter, Brivio *et al.* demonstrate another approach for MALDI-MS on-line analysis after microfluidic processing of chemical or biochemical samples; liquid actuation is triggered and driven by the vacuum environment present in the ionization source of the mass spectrometer and the microchip includes an open area (outlet reservoir or detection window) where samples can be irradiated by a laser. Finally, Nichols and Gardeniers describe a microfluidic dedicated to MALDI-MS analysis and kinetic studies of an enzymatic reaction; fluids are actuated and mixed extremely fast using the electrowetting-on-dielectric (EWOD) principle and analysis is performed off-line after quenching of the enzymatic reaction.

The last chapter of this book gives an example of the miniaturization of the analysis instrumentation, *i.e.* the mass spectrometer. Cotter *et al.* illustrate here the conception of a miniaturized MALDI-TOF mass spectrometer and its applications for homeland safety and clinical diagnostics purposes.

We hope you will enjoy this book, and we wish you lots of pleasure and inspiration reading this volume!

Séverine Le Gac and Albert van den Berg