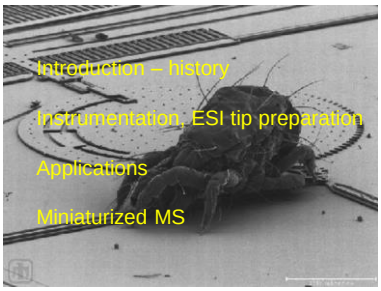
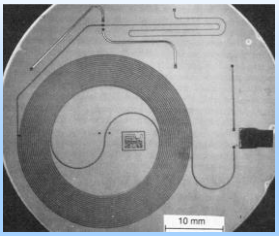
Micro(fluidic) mass spectrometry

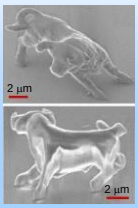


A Gas Chromatographic Air Analyzer Fabricated on a Silicon Wafer



Terry, S.C., Jerman, J.H., Angell, J.B. IEEE Transactions on Electron Devices, 1979, 26, 1880-86.

Microfabrication at subdifraction-limit resolution



780 nm, 150 fsec, Ti-saphire laser.

Raster scanning with two photon absorbtion - polymerization of SCR500 resin.

Spatial resolution 120 nm.

Kawata, S., Sun, H.-B., Tanaka, T. & Takada, K. Finer features for functional microdevices. Nature 412, 697 - 698 (2001).

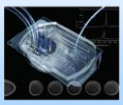
Basic Microfabrication Techniques

- ***Micromachining/Precision Machining***
  - High-precision Micromilling
  - Laser Ablation
  - ⇨ 10's μm
- ***Lithography***
  - Optical Lithography
  - X-ray Lithography
  - ⇨ 250 nm
  - E-beam Lithography
  - Ion Beam Lithography
  - ⇨ 5-10 nm
- ***Etching Techniques***
  - Dry and Wet Etching
  - ⇨ 10's nm
- ***Replication Techniques***
  - Hot-Embossing
  - Injection Molding
  - Casting
  - ⇨ 10's nm

Steven A. Soper, Univ. North Carolina, Chapel Hill

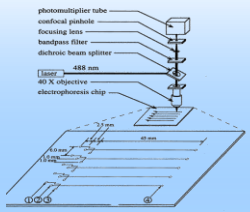
What Can Microfluidics Provide?

- Reduced processing time
- Process automation
- Point-of-Care (PoC) operation
- Assay reproducibility
- New processing capabilities
- Reduction in reagent/sample consumption
- But, be careful:
  - Scaling issues
  - Fabrication difficulties
  - Surface chemistry (high surface-to-volume ratio)
  - Sampling statistics



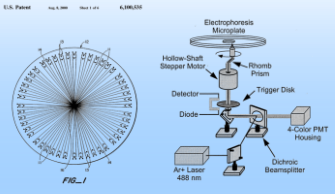
Steven A. Soper, Univ. North Carolina, Chapel Hill

Ultra-high-speed DNA fragment separations using microfabricated capillary array electrophoresis chips



Adam T. Woolley And Richard A. Mathies Proc. Natl. Acad. Sci. USA, vol. 91, pp. 11348-11352, 1994

Radial Capillary Array Electrophoresis Microplate and Scanner for High-Performance Nucleic Acid Analysis.

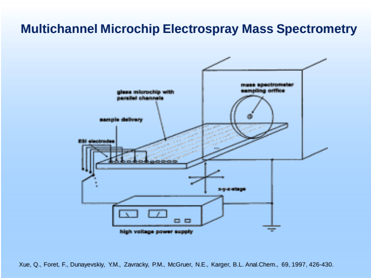


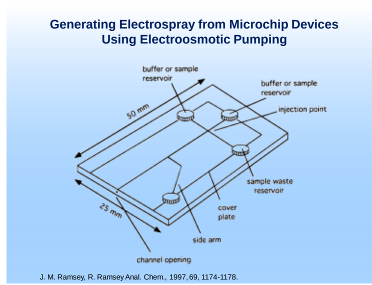
Yixing Shi, Peter C. Simpson, James R. Scherer, David Wexler, Christine Skibola, Maryon T. Smith, and Richard A. Mathies. Anal. Chem. 1999, 71, 5354-5361

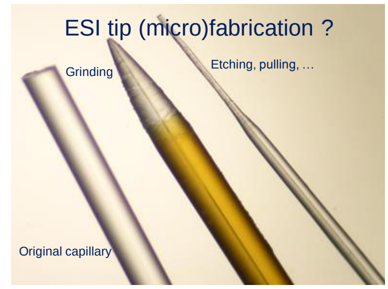
Microscale Fluid Handling System

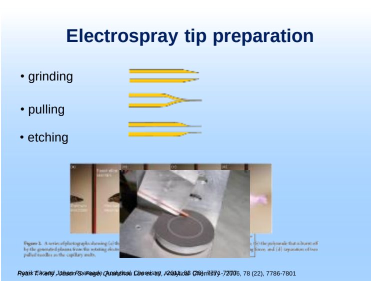
What is claimed is: 1. A liquid handling system, comprising a microscale liquid handling substrate having one or more channels integrally formed therein, for conducting a liquid sample in said substrate, said one or more channels terminating in one or more exit ports in an outer surface of said substrate for transfer of a microscale quantity of a liquid sample off said substrate by **droplet, spray or stream**;

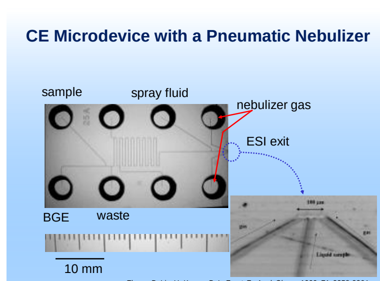
Karger, B.L., Foret, F., Qifeng, X., Dunayevskii, Y., Zavracki, P., McGruer, N. U.S. Patent # 5,872,010, 1999.

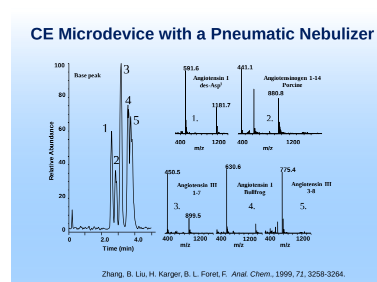

Multichannel Microchip Electrospray Mass Spectrometry
glass microchip with parallel channels
mass spectrometer sampling orifice
sample delivery
ESI electrodes
x-y-z stage
high voltage power supply
Xue, Q., Foret, F., Dunayevskiy, Y.M., Zavracky, P.M., McGruer, N.E., Karger, B.L. Anal.Chem., 69, 1997, 426-430.

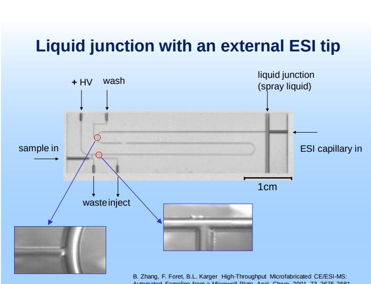

Generating Electrospray from Microchip Devices Using Electroosmotic Pumping
buffer or sample reservoir
buffer or sample reservoir
injection point
50 mm
25 mm
sample waste reservoir
cover plate
side arm
channel opening
J. M. Ramsey, R. Ramsey Anal. Chem., 1997, 69, 1174-1178.

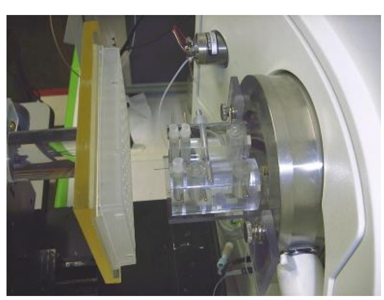

ESI tip (micro)fabrication ?
Grinding
Etching, pulling, …
Original capillary

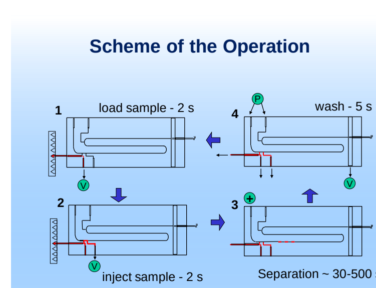

Electrospray tip preparation
• grinding
• pulling
• etching


CE Microdevice with a Pneumatic Nebulizer
sample
spray fluid
nebulizer gas
ESI exit
BGE
waste
10 mm
Zhang, B. Liu, H. Karger, B. L. Foret, F. Anal. Chem., 1999, 71, 3258-3264.

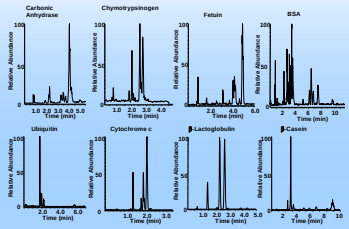

CE Microdevice with a Pneumatic Nebulizer
Base peak
Relative Abundance
Time (min)
m/z
Zhang, B. Liu, H. Karger, B. L. Foret, F. Anal. Chem., 1999, 71, 3258-3264.


Liquid junction with an external ESI tip
+ HV
wash
liquid junction (spray liquid)
sample in
ESI capillary in
1cm
waste
inject
B. Zhang, F. Foret, B.L. Karger High-Throughput Microfabricated CE/ESI-MS: Automated Sampling from a Microwell Plate. Anal. Chem. 2001, 73, 2675-2681

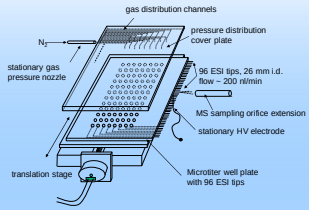



Scheme of the Operation
1
load sample - 2 s
4
wash - 5 s
2
inject sample - 2 s
3
Separation ~ 30-500 s

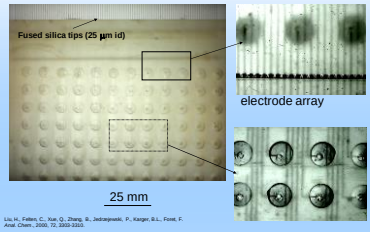
Protein Tryptic Digests



High Throughput ESI/MS Analysis

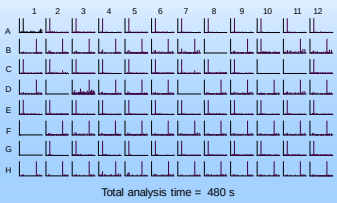


96 Tip Plastic Microdevice



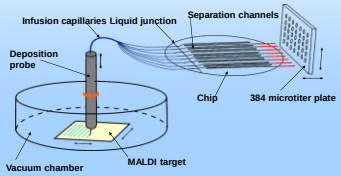
Liu, H., Felten, C., Xue, Q., Zhang, B., Jedrzejewski, P., Karger, B.L., Foret, F. *Anal. Chem.*, 2000, 72, 3303-3310.

High Throughput Analysis with 96 ESI Tips Microdevice

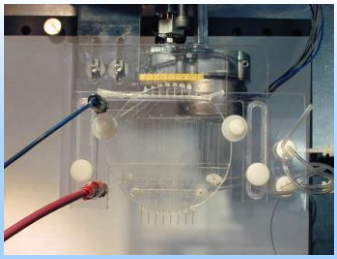


Total analysis time = 480 s

Vacuum Deposition MALDI With Multichannel CE Chip

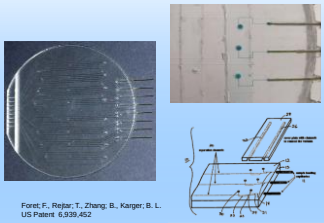


Rejtar, T., et al., unpublished



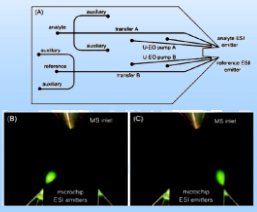
Rejtar, T., et al., unpublished

Parallel sample loading and injection device for multichannel microfluidic devices



Foret, F., Rejtar, T., Zhang, B., Karger, B. L. US Patent 6,939,452

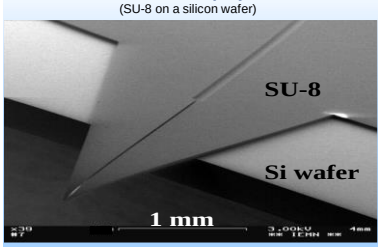
Microfluidic dual emitter electrospray ionization source for accurate mass measurements



A. G. Chambers and J. M. Ramsey, Anal. Chem., 2012, 84, 1446.

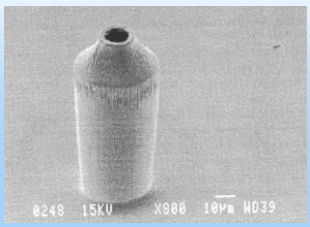
Micro-nib electrospray source

(SU-8 on a silicon wafer)



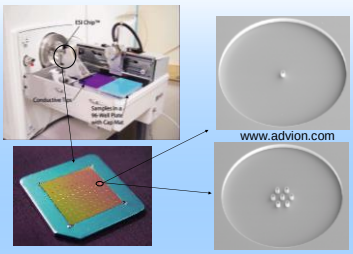
Le Gac S., Arscott S., Rolando C. ELECTROPHORESIS 2003, 24, 3640-3647.

ESI tips produced by DRIE in silicon

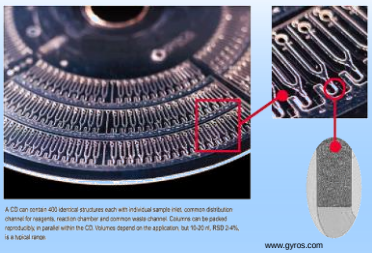


Sjödahl, J., Malm, J., Gröss, P., Emmer, A., Steenne, G., Roeraade, J. Rapid Commun. Mass Spectrom. 2003, 17, 337—341.

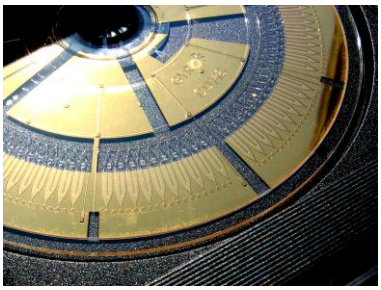
Infusion ESI Tip Array

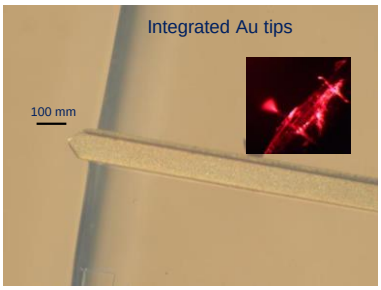


The CD microdevice concept

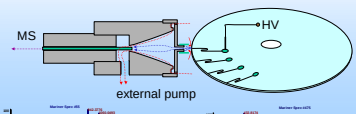


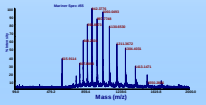
A CD can contain 400 identical structures each with individual sample inlet, common distribution channel for reagents, reaction chamber and common waste channel. Columns can be packed reproducibly, in parallel within the CD. Volumes depend on the application, but 10-20 nl, RSD 2-4%, is a typical range.

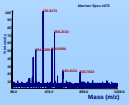




Aerodynamic mass spectrometry interfacing of microdevices without electrospray tips







10^{-6} M myoglobin in 50% IPA, 1% HAc

10^{-5} M Bradykinin, Angiotensin, Neurotensin in 50% ACN, 1% HAc

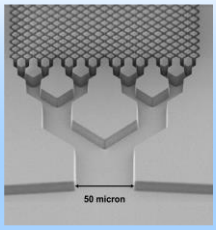
J. Grym, M. Otevrel, F. Foret Lab Chip, 2006, 6, 1306–1314

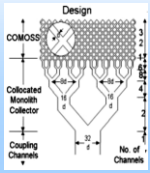
ESI tip fabrication

Applications

Microfabricated Monolith Columns for Liquid Chromatography

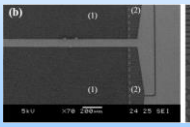
Sculpting Supports for Liquid Chromatography

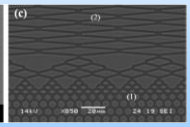




Fred E. Regnier J. High Resol. Chromatogr. **2000**, *23*, (1) 19–26

Porous-shell pillar array column separations on a capillary LC instrument



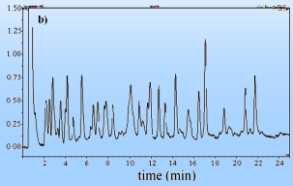


De Malsche W., De Bruyne S., Op de Beeck J., Eeltink S., Detobel F., Gardeniers H., Desmet G. Journal of Separation Science 2012, 35, 2010-17

De Malsche W., Op de Beeck J., De Bruyne S., Gardeniers H., Desmet G. Analytical chemistry 2012, 84(3), 1214-1219

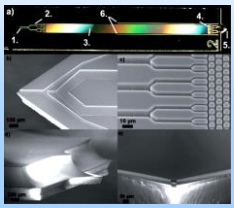
Gradient LC separation of albumin digest

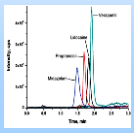
(4µl/min, 1 mg/ml, UV detection)



De Malsche W., De Bruyne S., Op de Beeck J., Eeltink S., Detobel F., Gardeniers H., Desmet G. Journal of Separation Science 2012, 35, 2010-2017

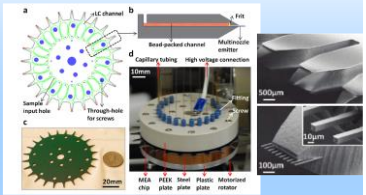
A microfabricated micropillar liquid chromatographic chip Monolithically integrated with an electrospray ionization tip





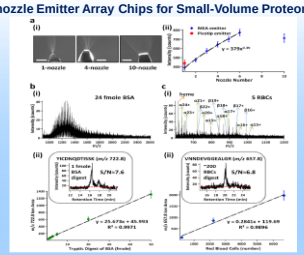
Lauri Sainiemi, Teemu Nissilä, Risto Kostiainen, Sami Franssila and Raimo A. Ketola Lab Chip, 2012, 12, 325

Multinozzle Emitter Array Chips for Small-Volume Proteomics



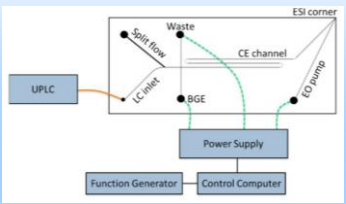
Mao, P; Gomez-Sjoberg, R; Wang, DJ. Anal. Chem. 2013, 85, 816-819.

Multinozzle Emitter Array Chips for Small-Volume Proteomics



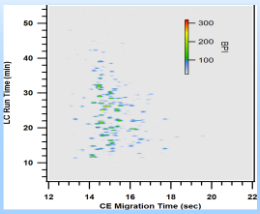
Mao, P; Gomez-Sjoberg, R; Wang, DJ. Anal. Chem. 2013, 85, 816-819.

Hybrid Capillary/Microfluidic System for Comprehensive Online Liquid Chromatography-Capillary Electrophoresis-ESI-MS



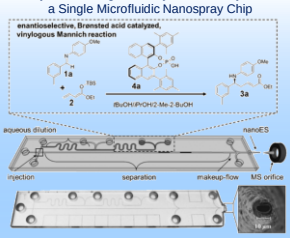
Mellors, JS; Black, WA; Chambers, AG; Starkey, JA; Lacher, NA; Ramsey, JM. Anal. Chem. 2013, 85, 4100-4106

Hybrid Capillary/Microfluidic System for Comprehensive Online Liquid Chromatography-Capillary Electrophoresis-ESI-MS



Mellors, JS; Black, WA; Chambers, AG; Starkey, JA; Lacher, NA; Ramsey, JM. Anal. Chem. 2013, 85, 4100-4106

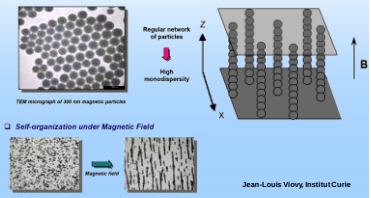
Asymmetric Organocatalysis and Analysis on a Single Microfluidic Nanospray Chip



S. Fritzsche, S. Ohla, P. Glaser, D. S. Giera, M. Sickert, C. Schneider and D. Belder Angew. Chem., Int. Ed., 2011, 50, 9467-9470.

Enzymatic microreactor with magnetic nanoparticles

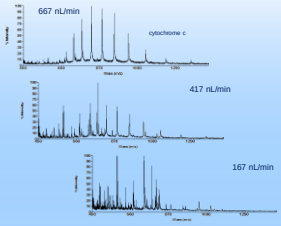
Self assembly of magnetic nanoparticles



❑ *Self-organization under Magnetic Field*

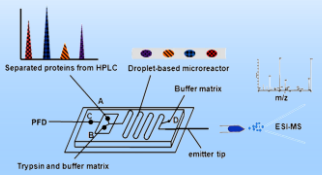
Jean-Louis Viovy, Institut Curie

On-chip tryptic digest with direct coupling to ESI-MS using magnetic particles



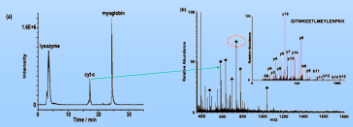
A. Le Nel, J. Krenkova, K. Klepárník, C. Smadja, M. Taverna, J.-L. Viovy, F. Foret Electrophoresis 2008, 29, 4944–4947

Proteolysis in microfluidic droplets: an approach to interface protein separation and peptide mass spectrometry



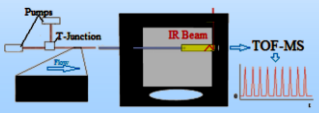
J. Ji, L. Nie, L. Qiao, Y. Li, L. Guo, B. Liu, P. Yang and H. H. Girault, Lab Chip, 2012, 12, 2625-2629.

Proteolysis in microfluidic droplets: an approach to interface protein separation and peptide mass spectrometry



J. Ji, L. Nie, L. Qiao, Y. Li, L. Guo, B. Liu, P. Yang and H. H. Girault, Lab Chip, 2012, 12, 2625-2629.

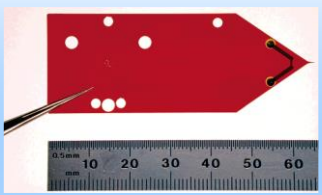
Nanoliter Segmented-Flow Sampling Mass Spectrometry with On-Line Compartmentalization



M. Volný, J. Rolfs, B. Hakimi, P. Fryčák, T. Schneider, D. Liu, G. Yen, D.T. Chiu, F. Tureček Anal. Chem., 2014, 86, 3647−3652

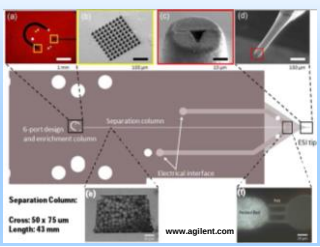
Commercialization

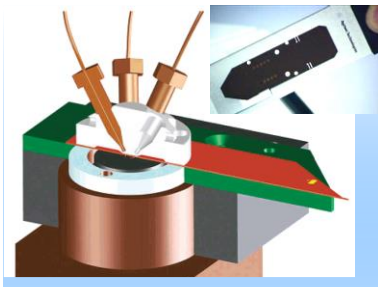
Microfluidic Chip for Peptide Analysis with an Integrated HPLC Column, Sample Enrichment Column, and Nanoelectrospray Tip



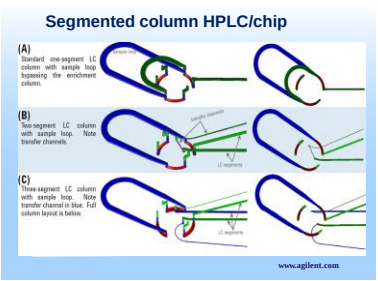
H. Yin, K. Killeen, R. Brennen, D. Sobek, M. Werlich, T. van de Goor Anal. Chem. 2005, 77, 527-533

Polyimide HPLC-chip, integrating an enrichment column, frits, a laser ablated ESI tip and trapazoidal separation column



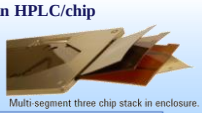


Segmented column HPLC/chip

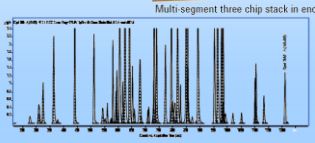


Segmented column HPLC/chip

Three LC columns – length 130 mm
Each segment individually packed.



Multi-segment three chip stack in enclosure.



BSA digest separated with a 30min gradient on a 2 column segmented chip, packed with 3.5µm particles

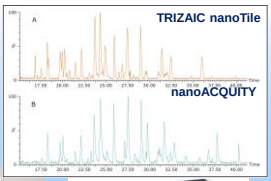
www.agilent.com

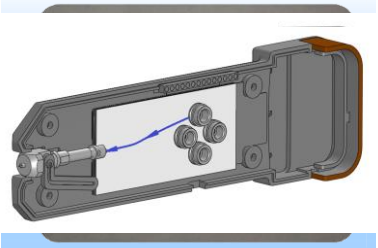
TRIZAIC nanoTile - Waters

- UPLC Performance
- All fluidic connections are pre-made & factory tested
- Integrated ESI Emitter
- Low System Volumes
- Decreased Band Broadening
- Higher Sensitivity
- Incorporates:
  - Heater & Sensor
  - EPROM
- Increased Reproducibility

Enolase digest

70 fmol, 2 µm particles





Green tape

Al_2O_3–MgO–SiO_2 glass particles mixed with organic binders and solvents to form glass ceramic

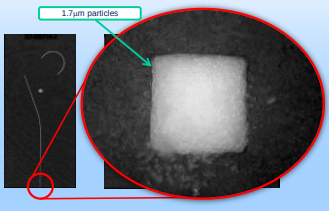
Product Description
951 Green Tape is a low-temperature cofired ceramic tape.
The 951 system comprises a complete cofireable family of Au and Ag metallizations, buried passives, and encapsulants.
951 is available in multiple thicknesses for use as an insulating layer in:

•Multichip modules
•Single chip packages
•Ceramic printed wiring boards
•RF modules

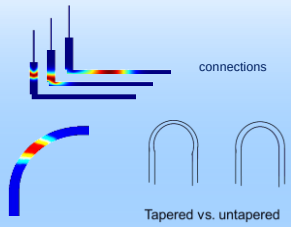
http://www.dupont.com/mcm

Ceramic Microfluidic Fabrication

Channel Geometries and Packing



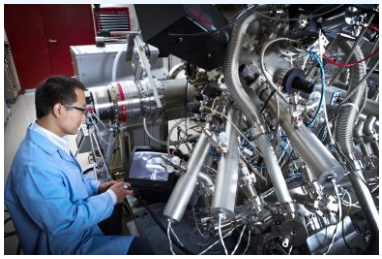
Channel shape effect



Packed glass LC chip

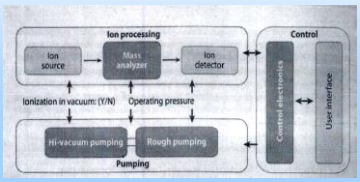
Eksigent, part of AB SCIEX, www.eksigent.com

Miniaturized (microfabricated) mass spectrometers?

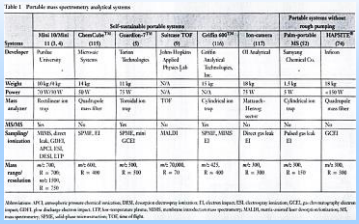


Miniaturized (microfabricated) mass spectrometers

Miniature Mass Spectrometers

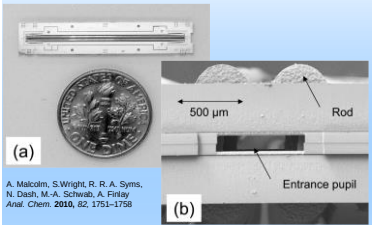


Ouyang Z., Cooks, G.R., Annu.Rev.Anal.Chem. 2009, 2, 187-214.

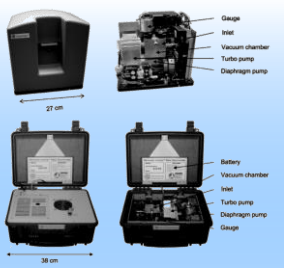


Ouyang Z., Cooks, G.R., Annual Rev.Anal.Chem. 2009, 2, 187-214.

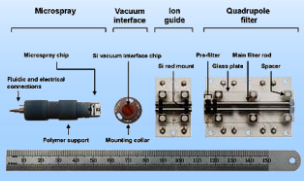
Miniature Mass Spectrometer Systems based on a Microengineered Quadrupole Filter



A. Malcolm, S.Wright, R. R. A. Syms, N. Dash, M.-A. Schwab, A. Finlay *Anal. Chem.* **2010**, *82*, 1751–1758



A miniature mass spectrometer for liquid chromatography applications



Rapid Communications in Mass Spectrometry
Volume 25, Issue 21, pages 3281-3288, 3 OCT 2011 DOI: 10.1002/rcm.5230
http://onlinelibrary.wiley.com/doi/10.1002/rcm.5230/full#rcm5230-fig-0002