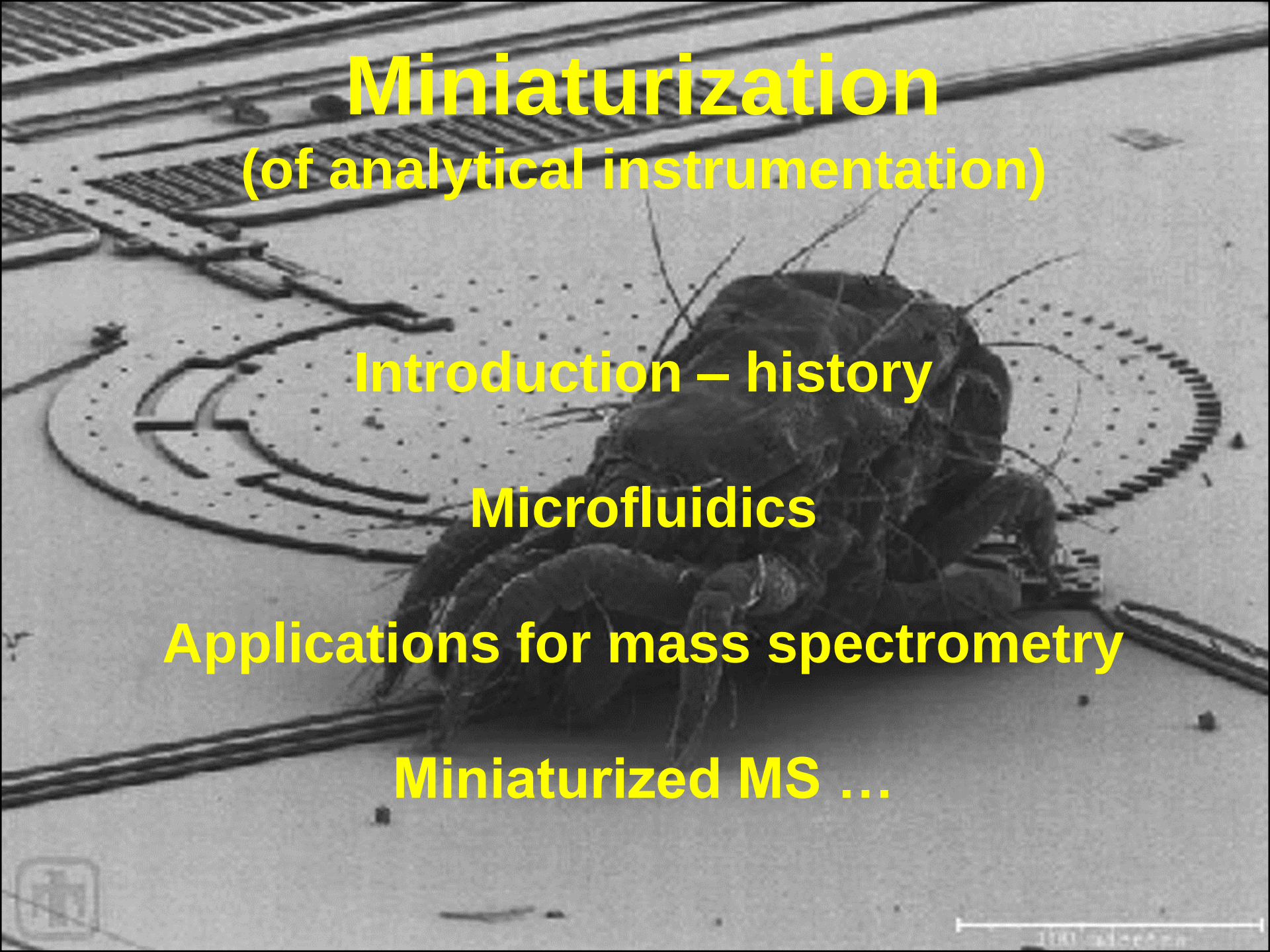


Miniaturization
(of analytical instrumentation)

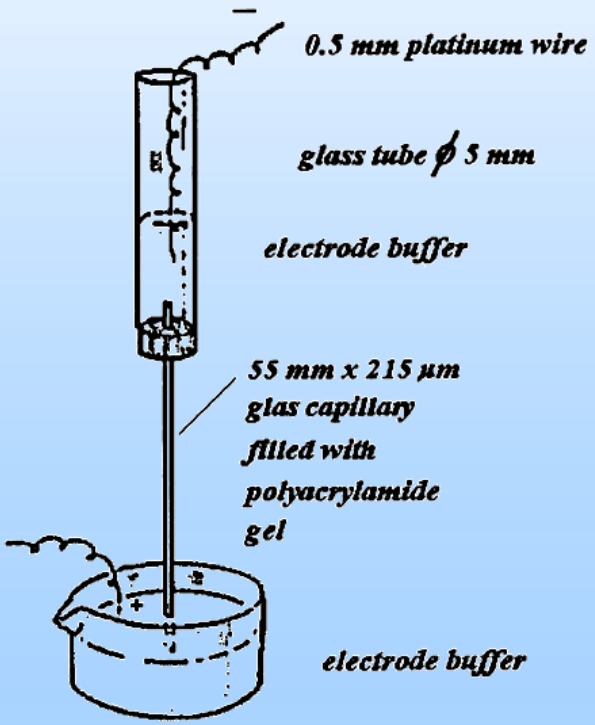
Introduction – history

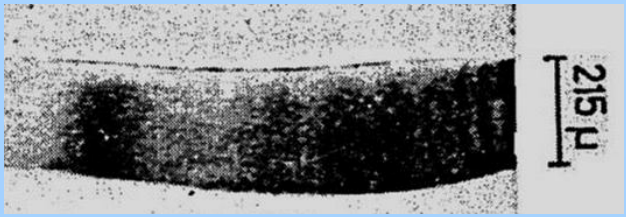
Microfluidics

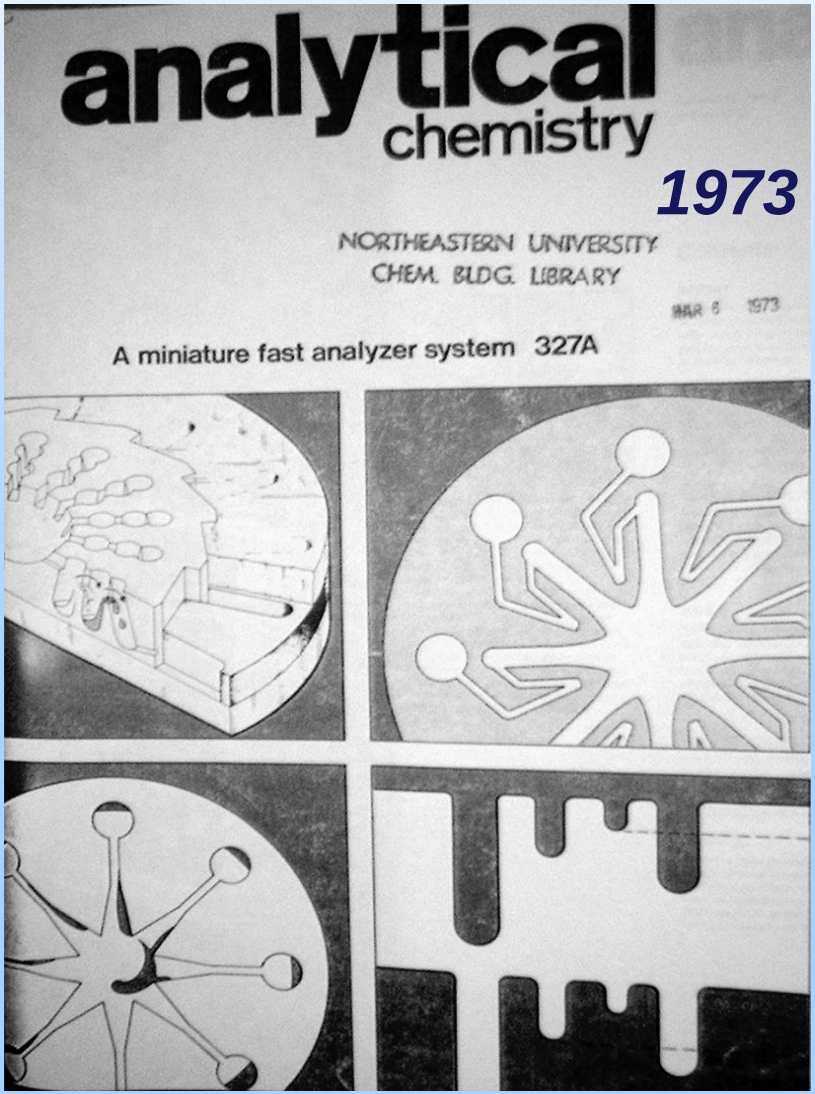
Applications for mass spectrometry

Miniaturized MS …

Instrumentation Miniaturization





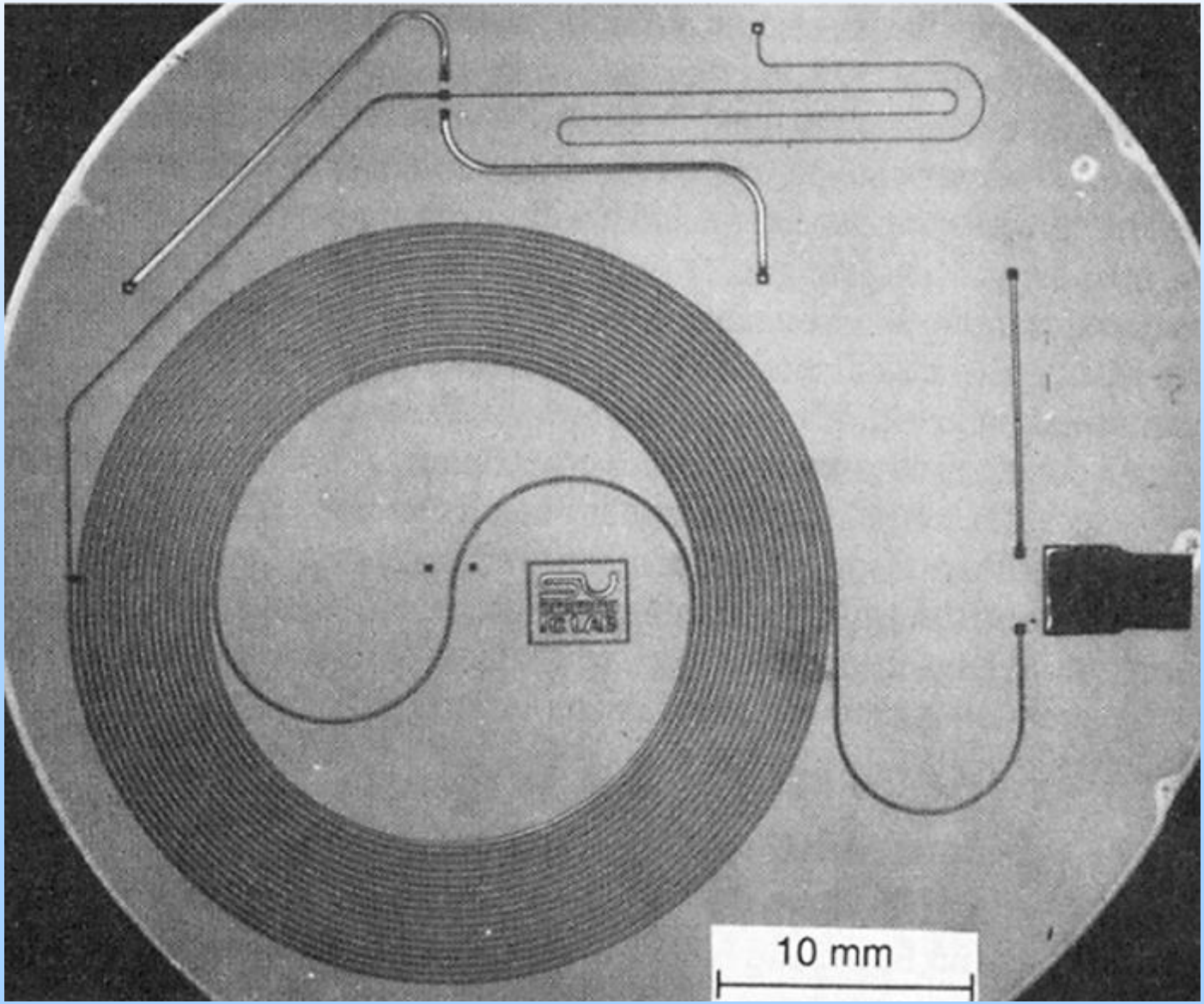


Capillary gel electrophoresis

Separation of nerve cell proteins

H. Hydén et al. Anal.Biochem, 17, 1-15, 1966.

A Gas Chromatographic Air Analyzer Fabricated on a Silicon Wafer



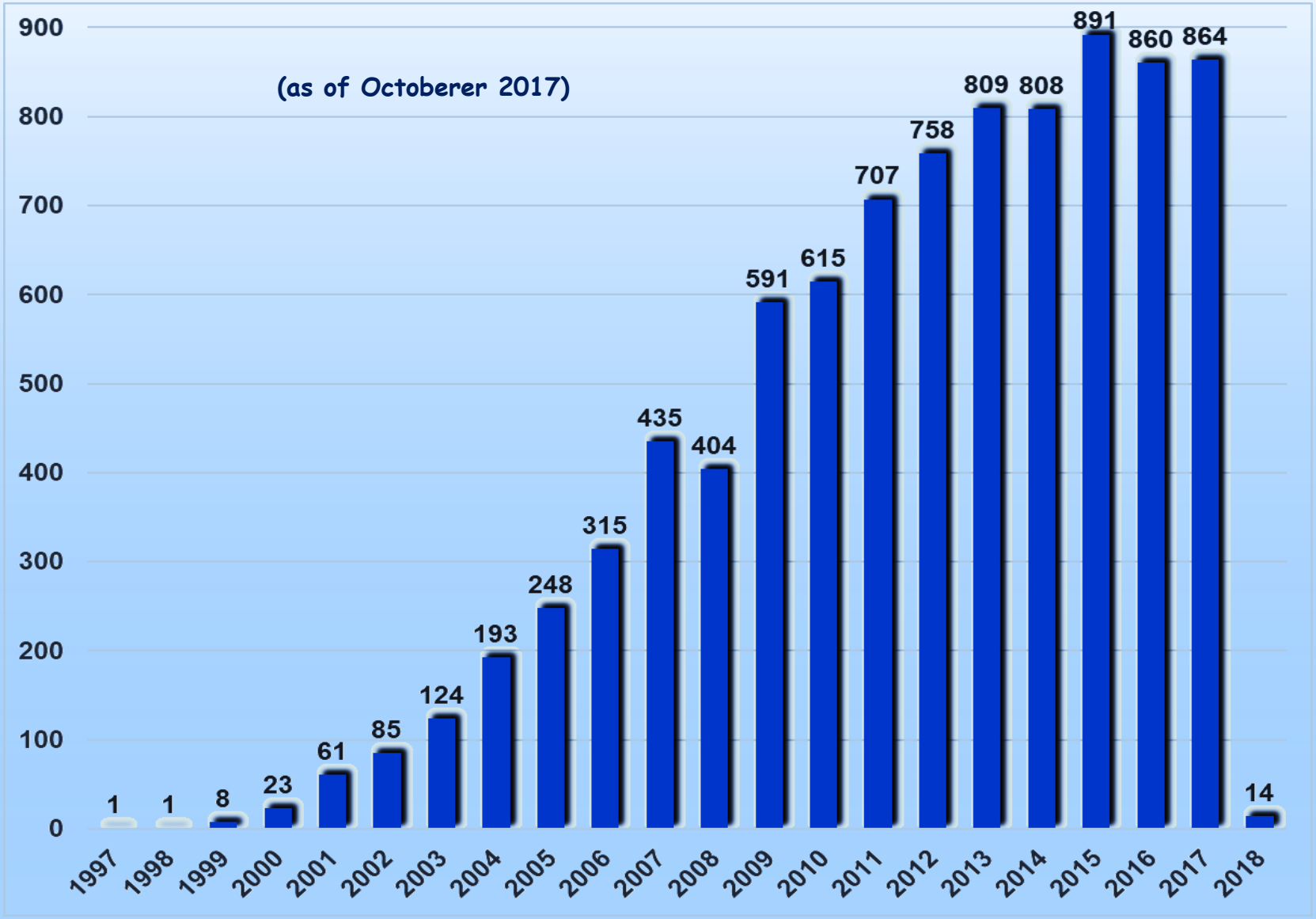
Terry, S.C., Jerman, J.H., Angell, J.B. IEEE Transactions on Electron Devices, 1979, 26, 1880-86.

There really is nothing new under the Sun

Prototype analog pneumatic computer to operate in a nuclear attack
NBS (now NIST) 1950's

Picture by Wyatt Vreeland, NIST

Incidence of the word "MICROFLUIDIC" in PubMed

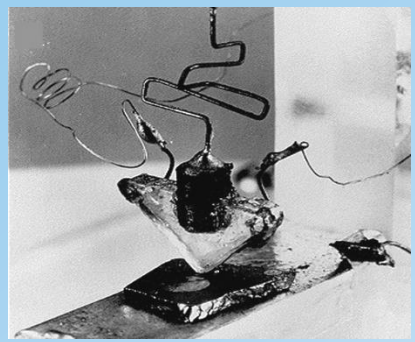


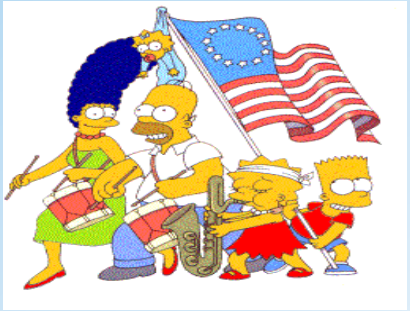
https://www.ncbi.nlm.nih.gov/pubmed?term=Microfluidic%5BTitle%5D

Microfluidics?

Microelectronics

Control of electric current





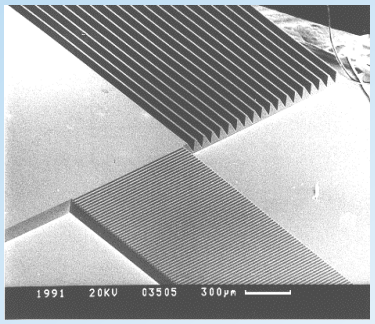
Technology

Products

Consequences

Microfluidics

control of fluid flows



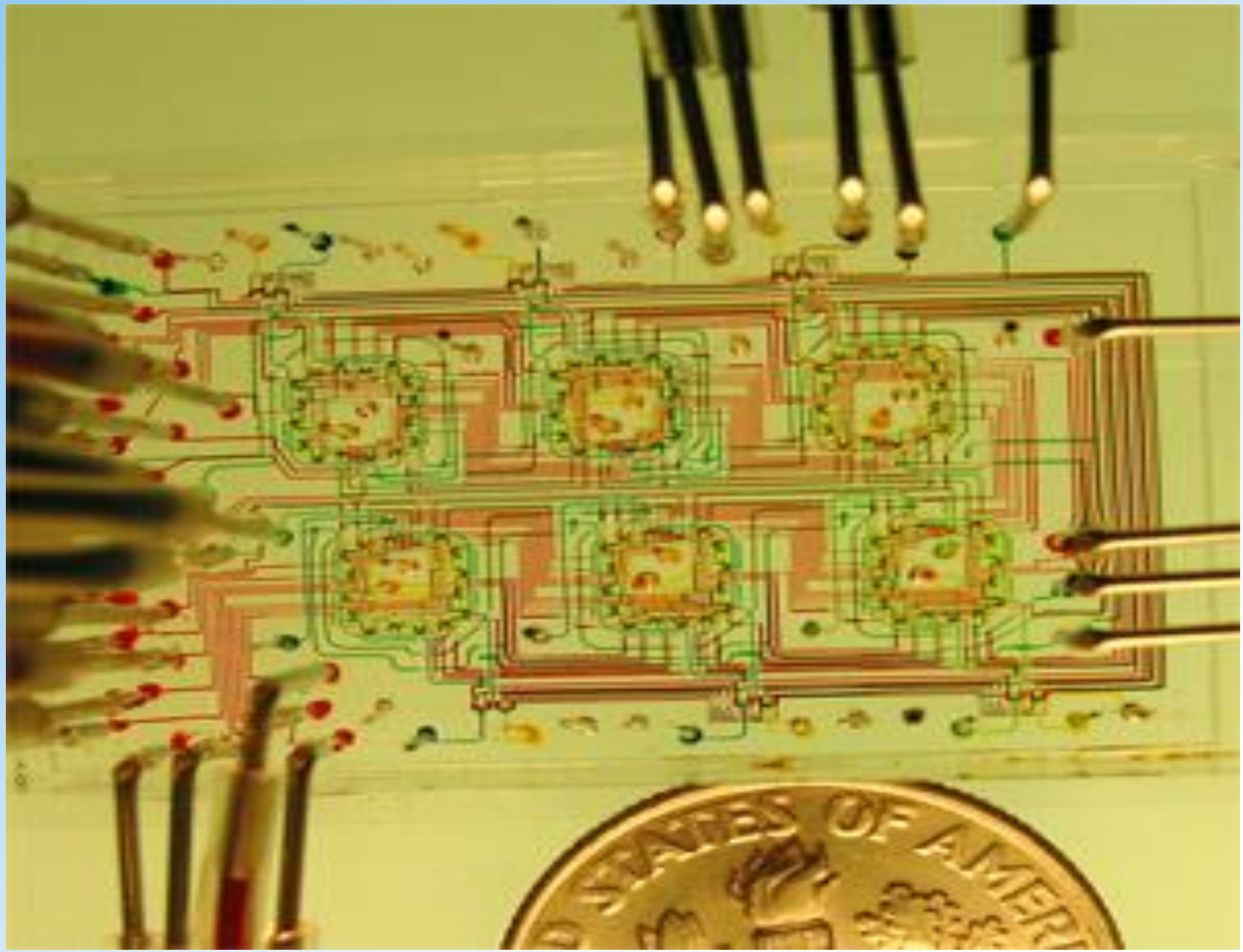
?

Speed of analysis

Space saving

Cost cutting

Mass production



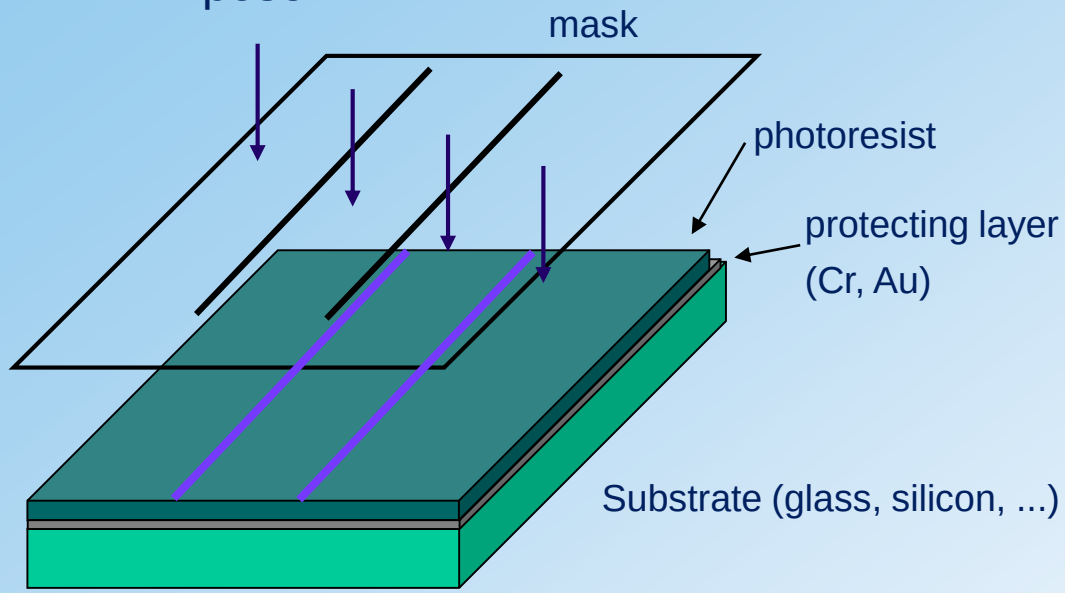
Stephen Quake, Dept. Bioengineering, Stanford University, http://thebigone.stanford.edu/index.html

Microfabrication technology

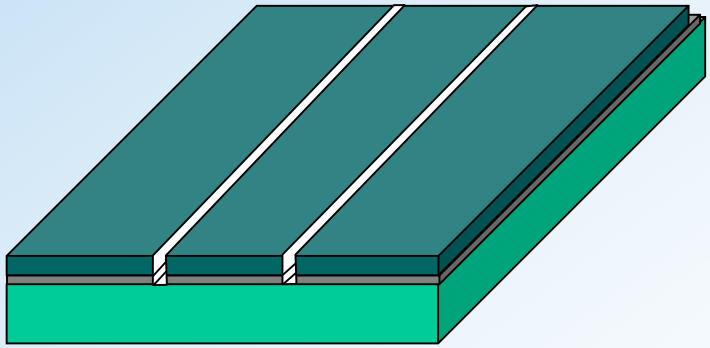
Micromilling	10 μm
Optical lithography	200 nm
e/ion beam lithography Multiple exposure techniques	10 nm
Etching (resist dependent)	~ nm
Replication (mass production) Injection molding Hot embossing Casting	10’s nm

Photolithography

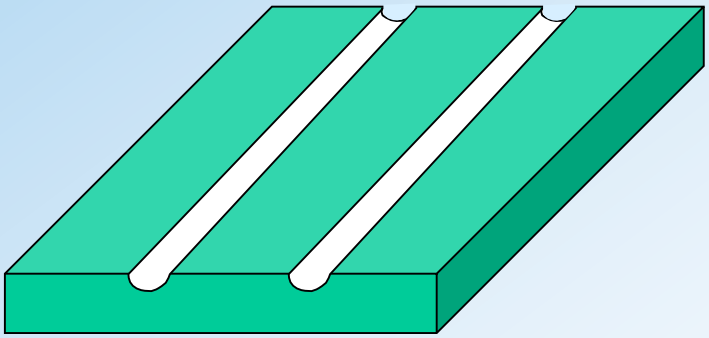
1. Expose



2. develop and etch

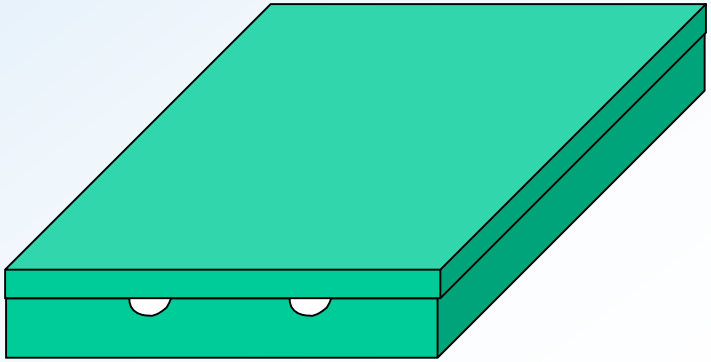


3. Remove the protection layer

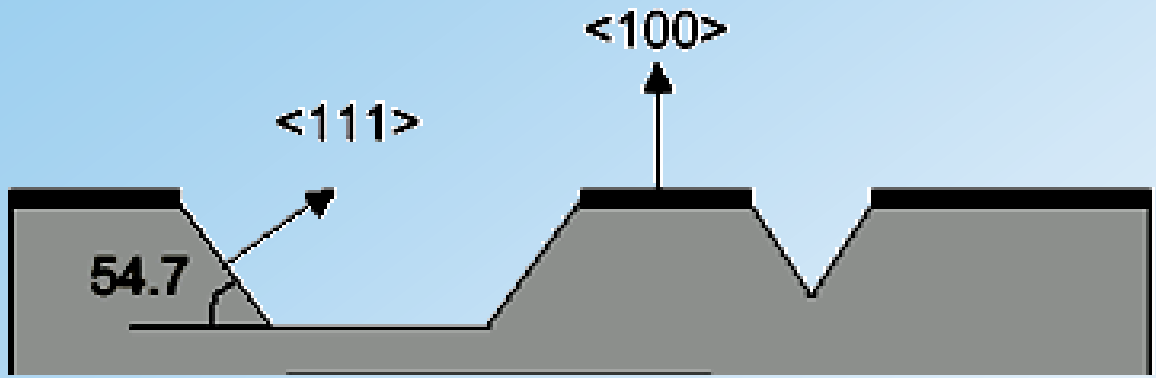


4. Close the structure

(thermal bonding)



SILICON - ANISOTROPIC ETCHING



* Anisotropic etching – direction dependent etch rate

* Etch rate slower perpendicularly to the crystalline planes with the highest density

* Typical etches: KOH, Tetramethyl Ammonium Hydroxide (TmAH) Ethylene Diamine Pyrocatechol (EDP)

Making and inspecting semiconductor chips requires pushing laser techniques deeper into the ultraviolet.

by Hank Hogan, Contributing Editor

As semiconductor feature sizes shrink, manufacturers need a light touch — and at the right wavelength. A look at three areas — lithography, metrology and assembly — shows how photonics-based innovations are tackling some of the semiconductor industry's most pressing problems.

Steppers are among the most critical tools used for semiconductor manufacturing and are at the heart of the photolithographic process, which transfers the features that are on a mask onto the photoresist material on a wafer. Subsequent processing reproduces that transferred layout in layers of conductors and insulators that eventually comprise a functioning integrated circuit. Today, state-of-the-art features are as small as 65 nm. Soon, they will be 45 nm, and the generation beyond that, 32 nm. The latter two scales are several years away, although the equipment needed for them is being rolled out now.

Although designed for manufacturing on a microscopic scale, the latest lithography stepper lens from Carl Zeiss SMT AG of Oberkochen, Germany, is not small. The Starlith 1900i weighs more than a metric ton, stands several feet tall and is as big around as a tree trunk. A catadioptric lens consisting of reflecting mirrors and refractive optics, it enables volume semiconductor production

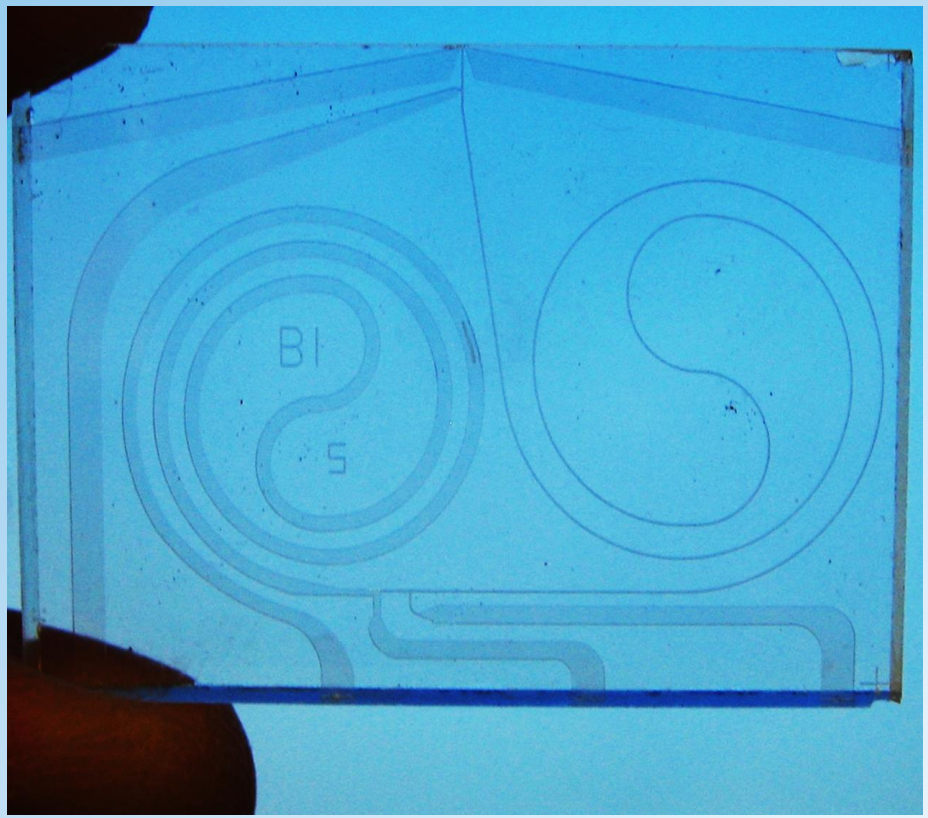
The device pictured is a catadioptric lens that, according to the manufacturer, can achieve 40-nm-resolution lithography on semiconductor chips. Courtesy of Carl Zeiss SMT.

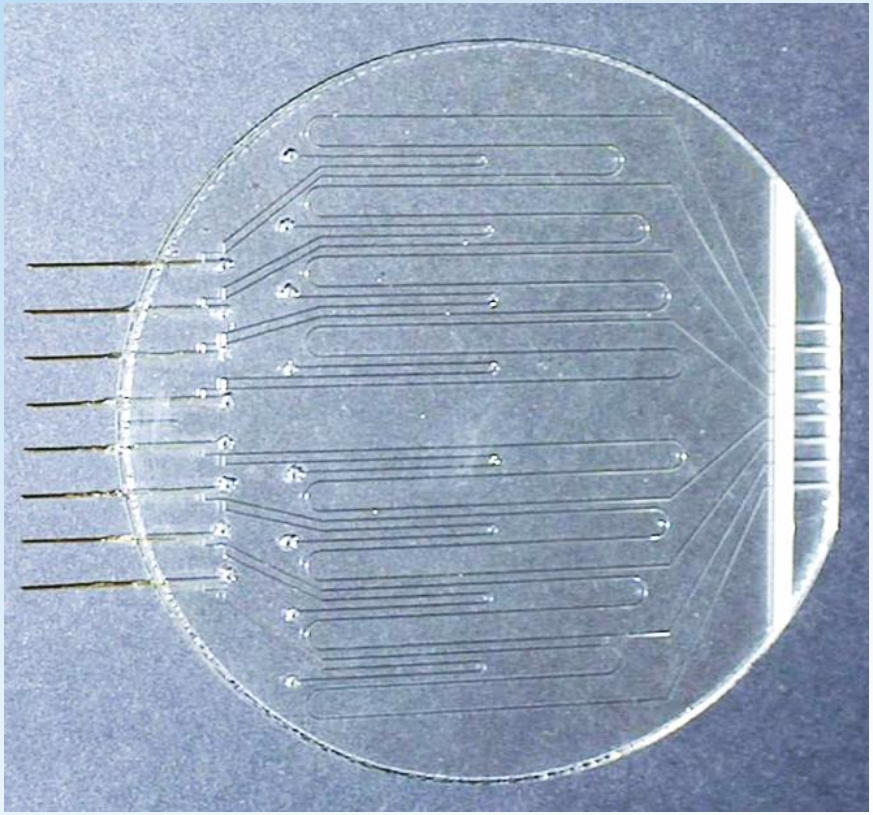
µPG 101 Tabletop Laser Pattern Generator

HEIDELBERG INSTRUMENTS

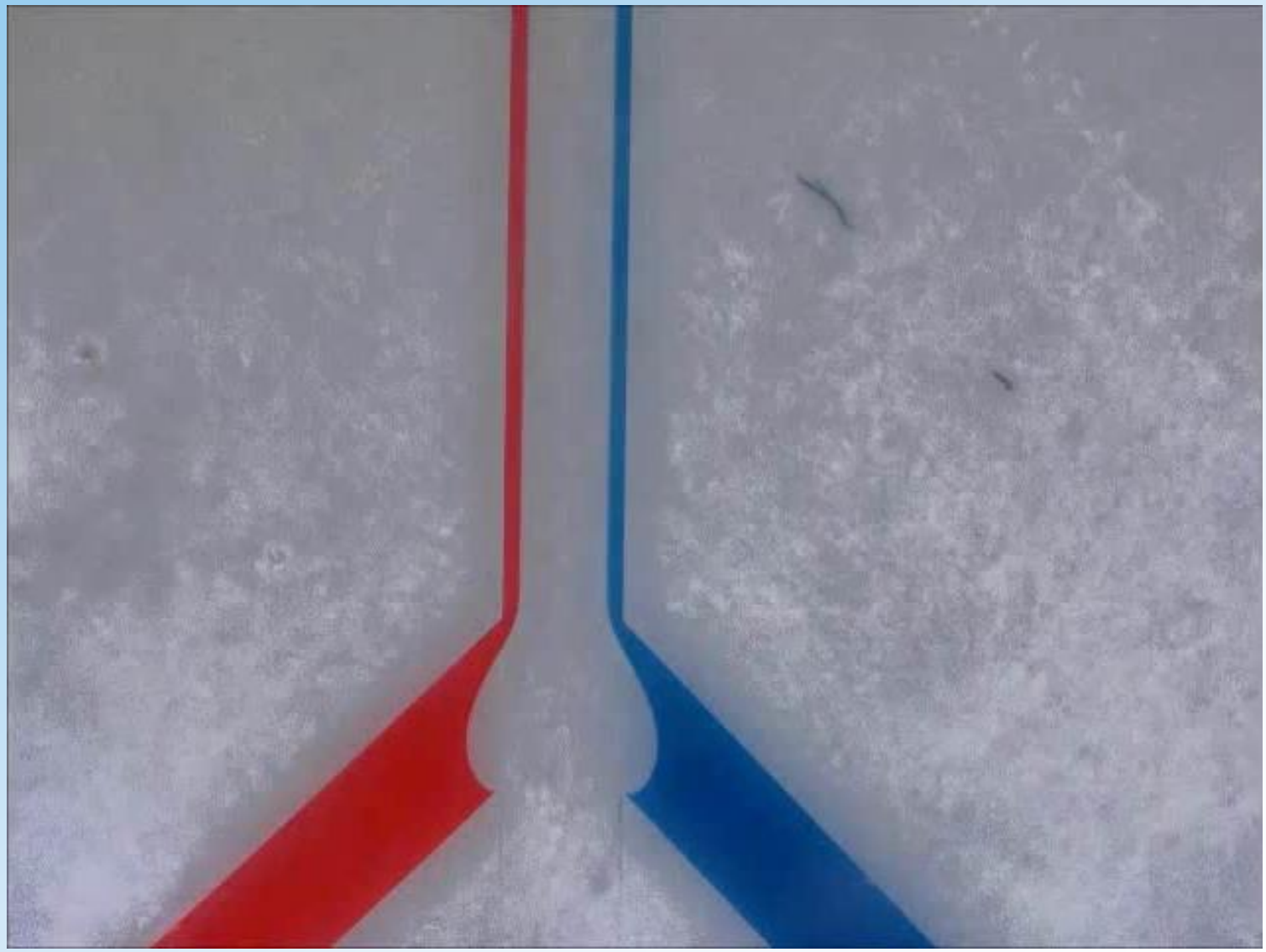
- Substrates up to 100 x 100 mm2
- Structures down to 1 µm
- Address grid down to 40 nm
- Standard or UV laser source

System Integration

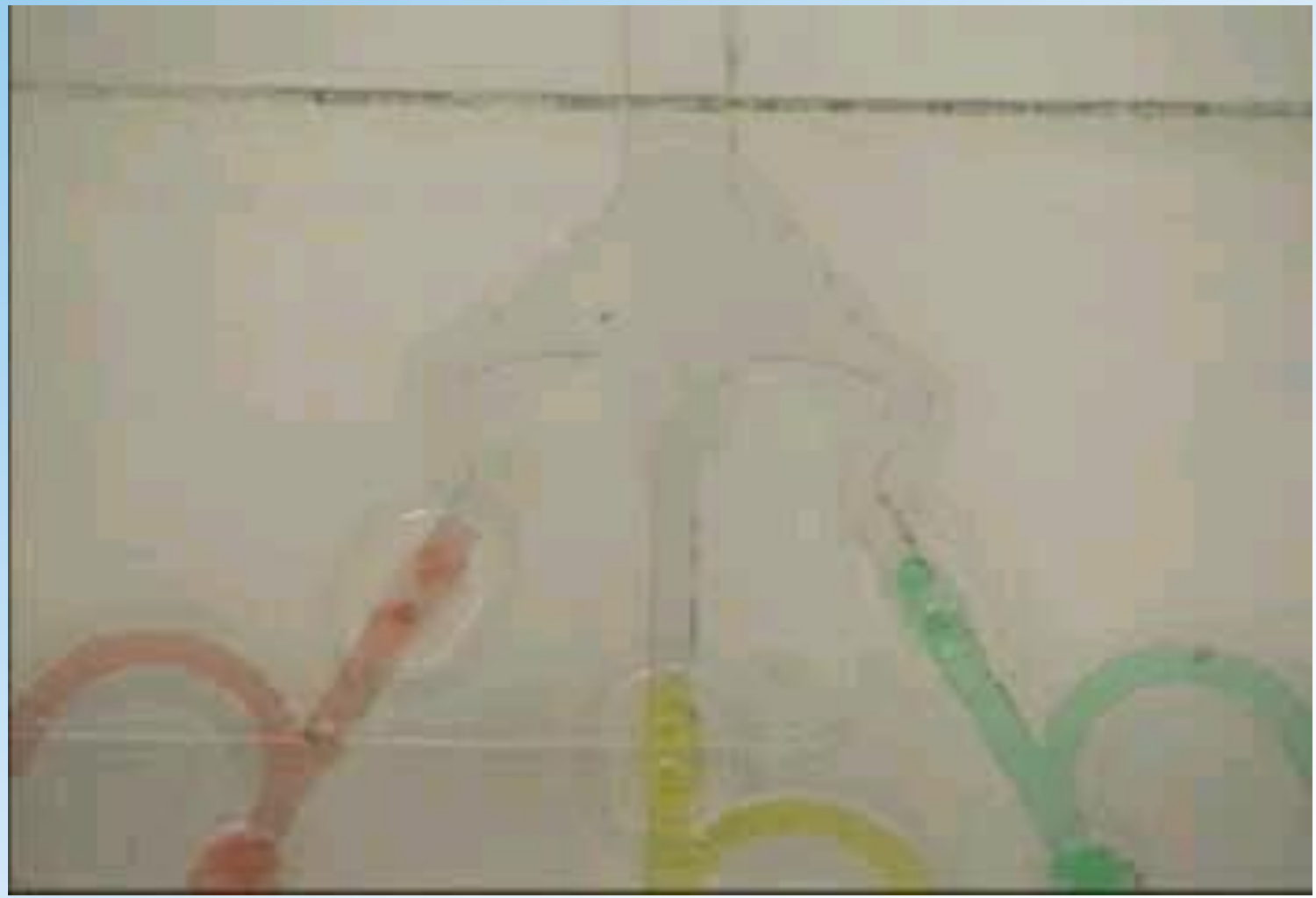




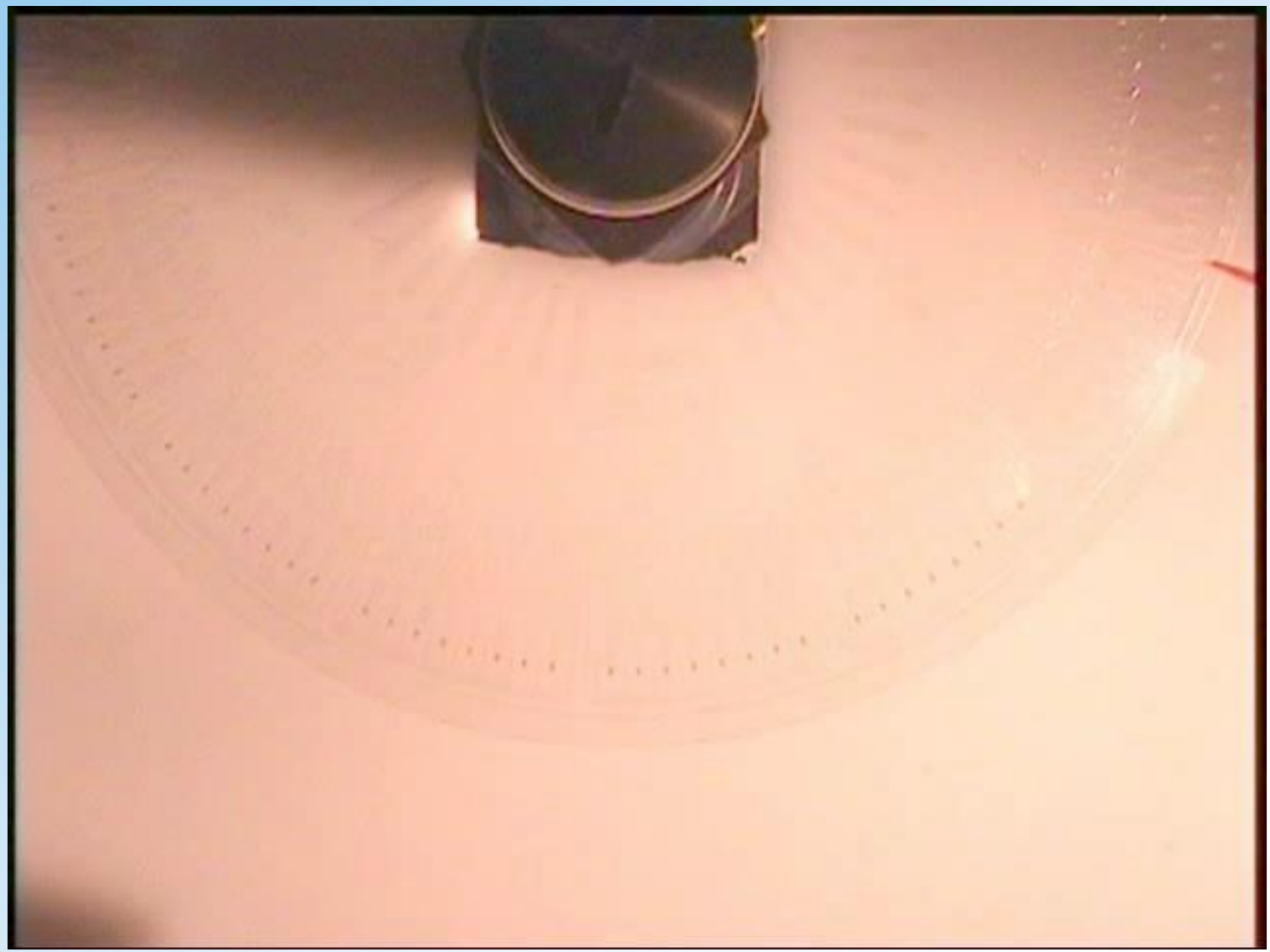
Spatial flow focusing



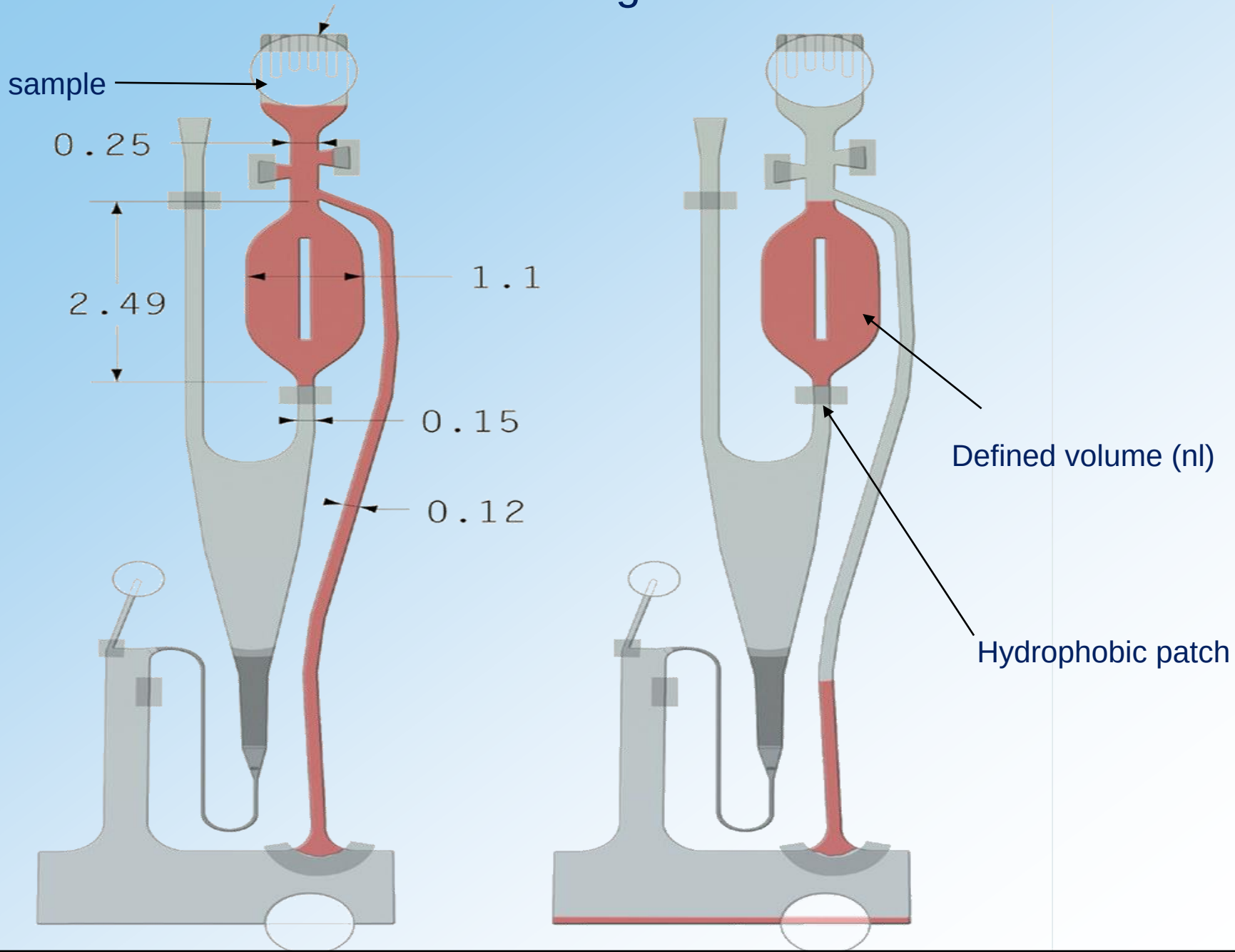
Diffusion limited mixing



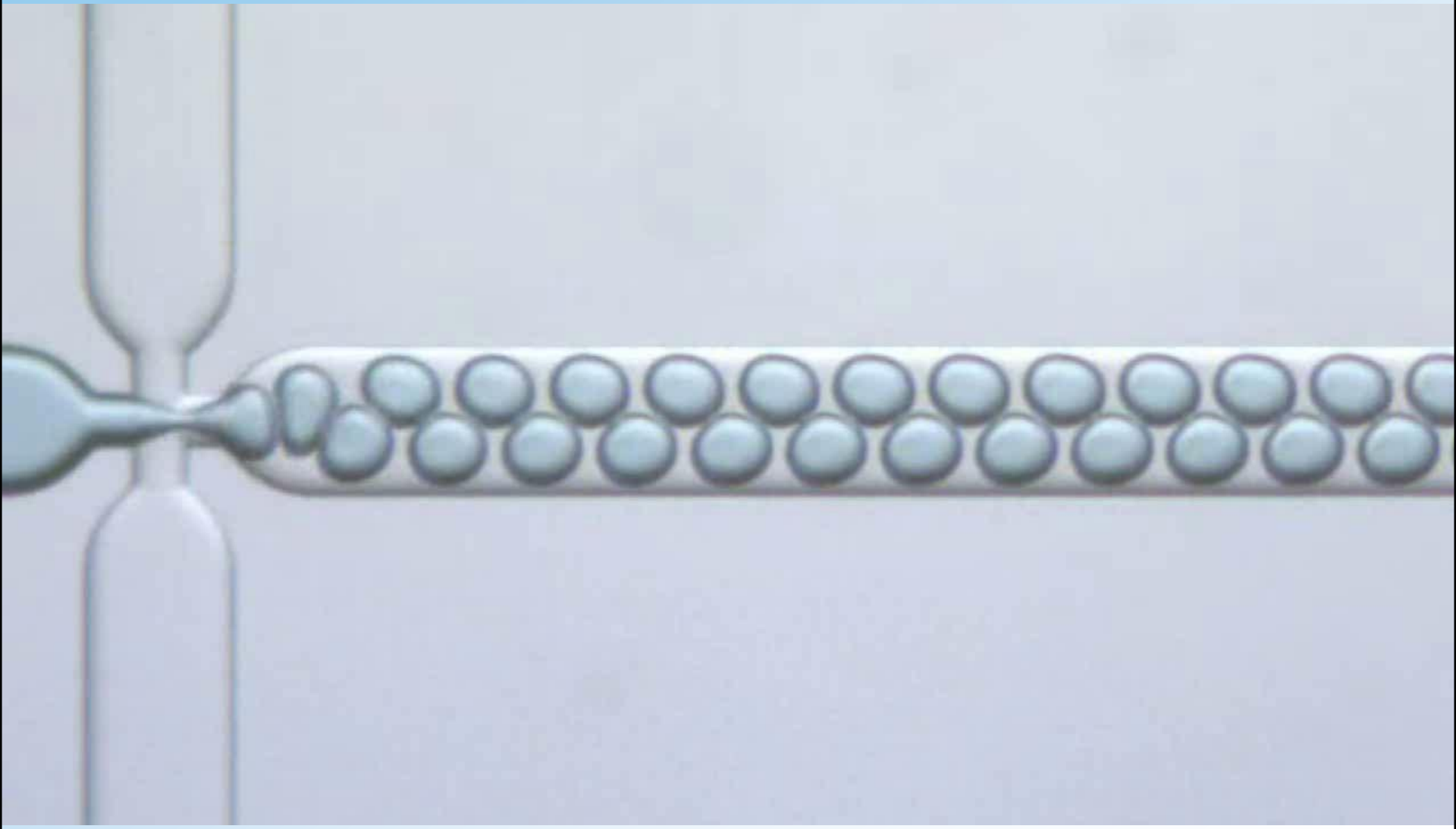
Capillary force filling



Exact volume metering on the nl level



Droplet generation in nl-pl volumes



http://www.dolomite-microfluidics.com/

Seth Fraden et al., J. AM. CHEM. SOC. 2007, 129, 8825-8835.

Benefits and Issues

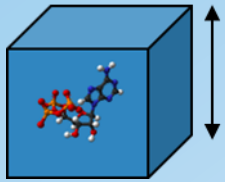
Size - space saving
Low reagent/sample consumption
Smaller size – faster analysis
Microchannel junctions without dead volume
Parallel systems for high throughput
Disposable parts - point-of-care devices

BUT

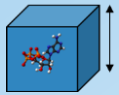
Scaling issues
Fabrication limitations
Surface chemistry
Concentration limits of detection
Phenomena unimportant on the macro scale may dominate

Small volume problem

Example: LOD = 1000 molecules



2.15 mm => 10 μl ~ 10^{-15} M



1 mm => 1 μl ~ 10^{-14} M

0.1 mm => 1 nl ~ 10^{-11} M

0.001 mm => 1 fl ~ 10^{-5} M

MICROFABRICATED DEVICES

* Sensors - accelerometers, glucose monitors, ...

* Genomics - first commercial applications

* Proteomics - sample processing
separation

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

U.S. Patent Aug. 8, 2000 Sheet 1 of 6 6,100,535

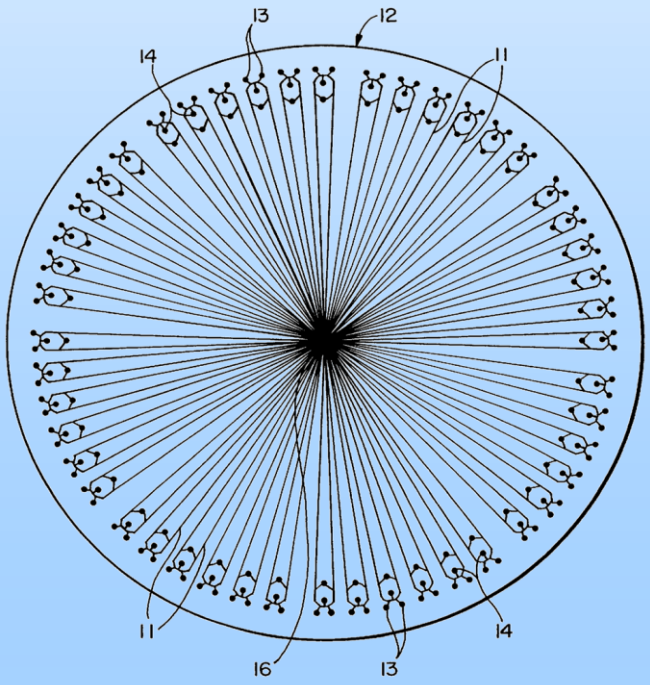
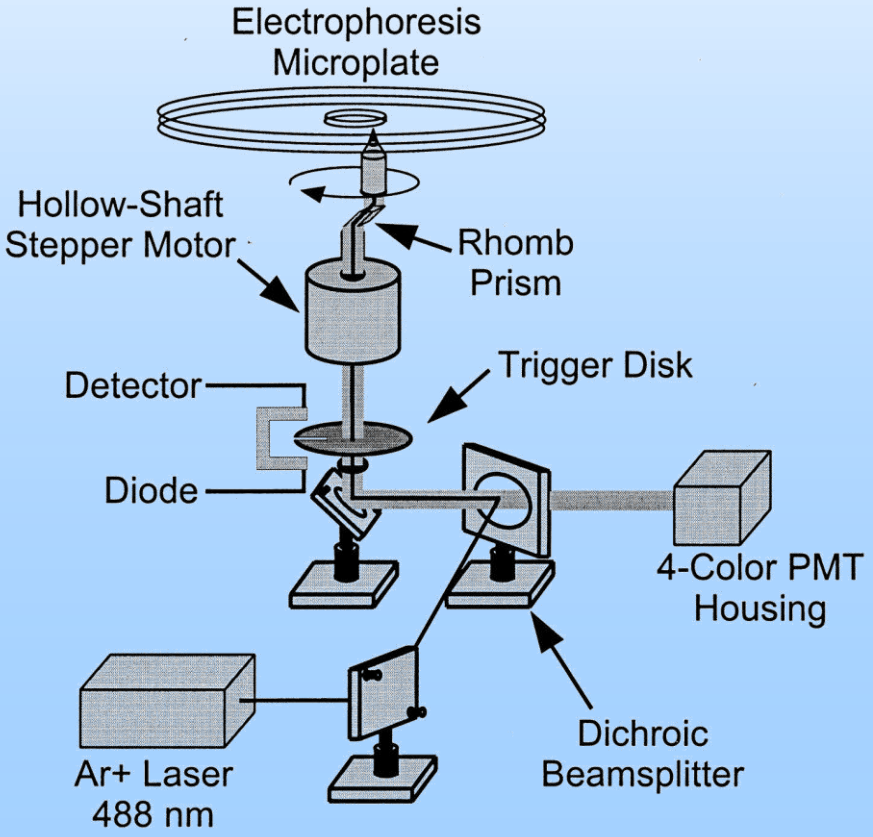


FIG_1



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

Microscale Fluid Handling System

U.S. Patent Feb. 16, 1999 Sheet 1 of 15 5,872,010

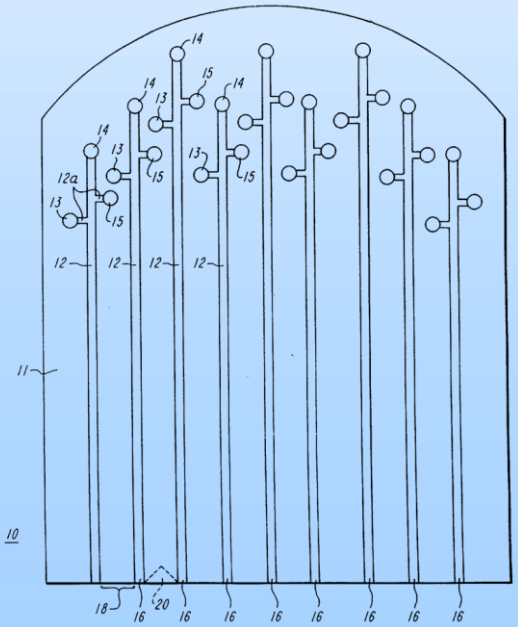


FIG. 1A

U.S. Patent Feb. 16, 1999 Sheet 4 of 15 5,872,010

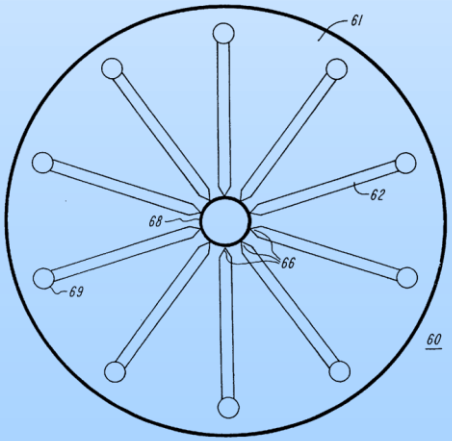


FIG. 3

U.S. Patent Feb. 16, 1999 Sheet 6 of 15 5,872,010

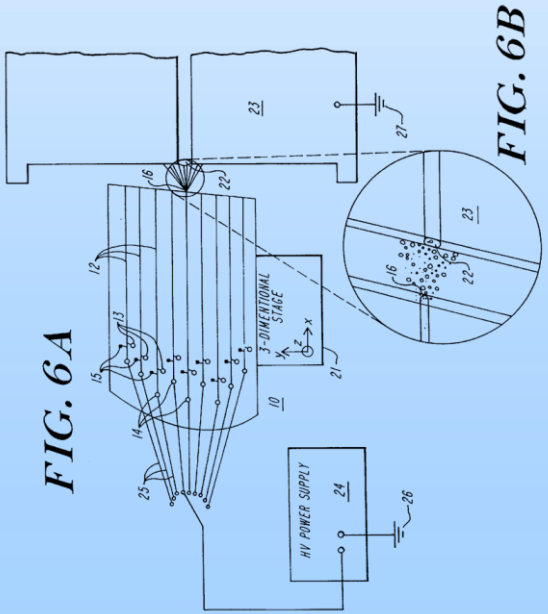


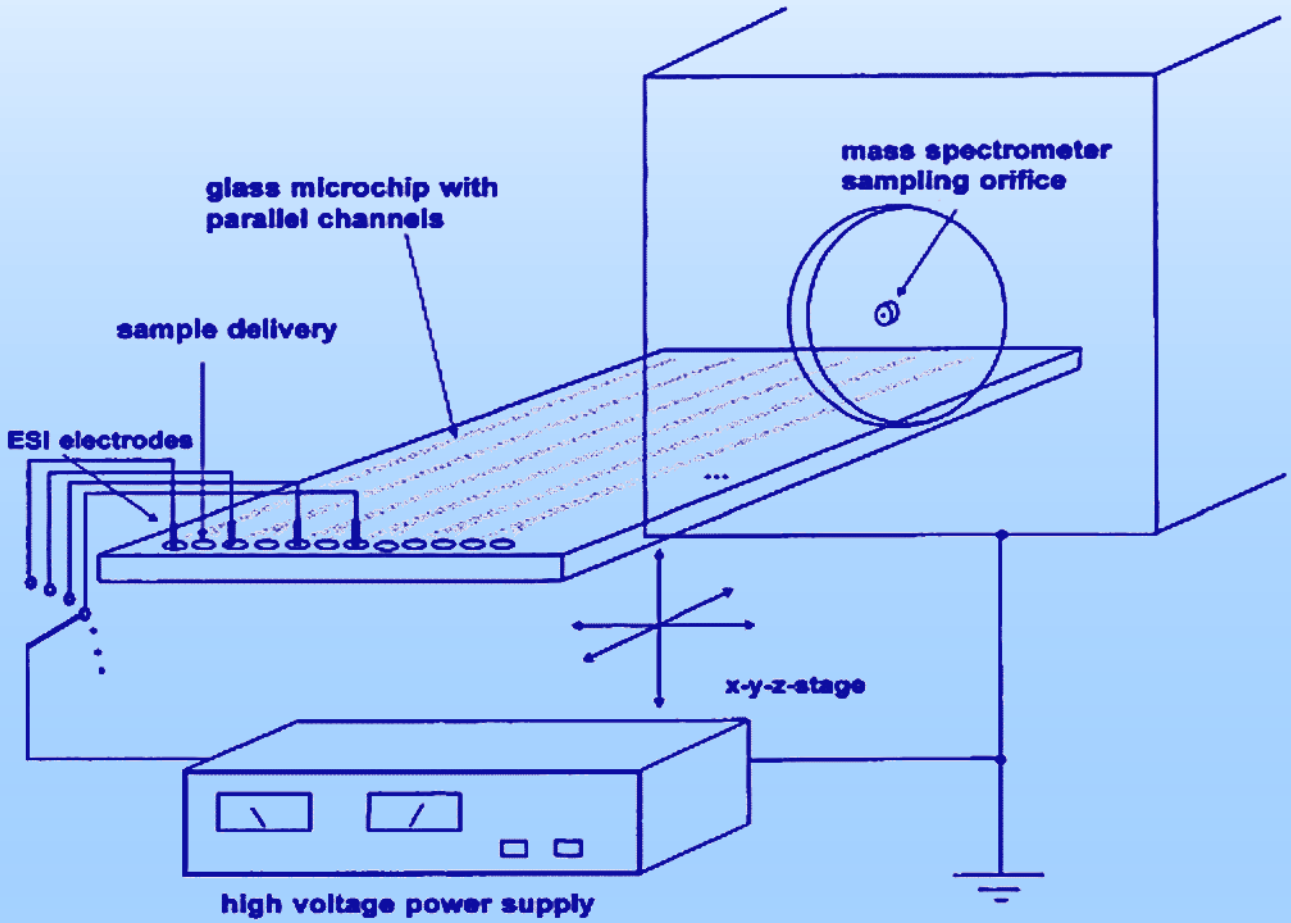
FIG. 6A

FIG. 6B

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**;

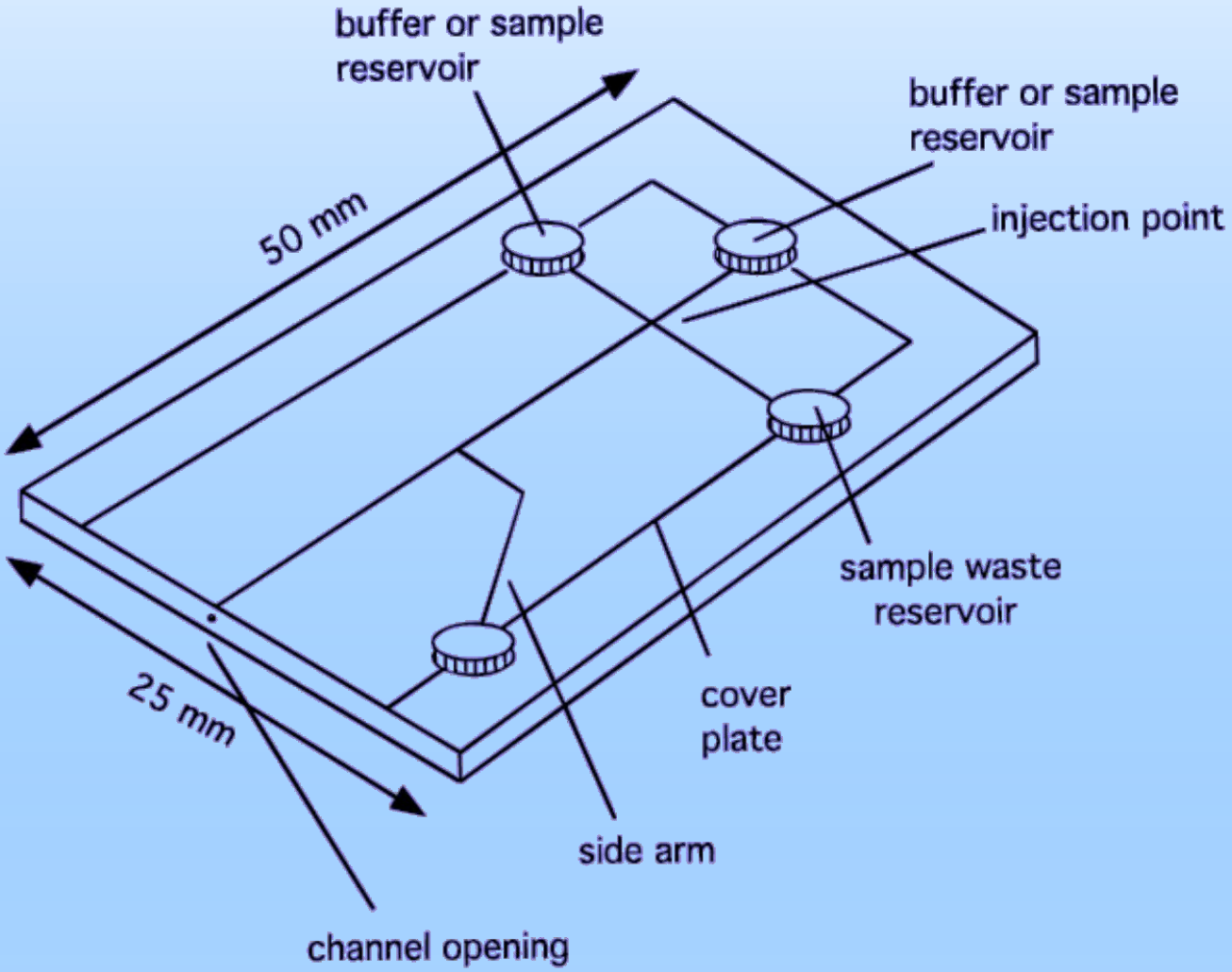
Karger, B.L., Foret, F., Qifeng, X., Dunayevski, Y., Zavracki, P., McGruer, N. U.S. Patent # 5,872,010, 1999.

Multichannel Microchip Electrospray Mass Spectrometry



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



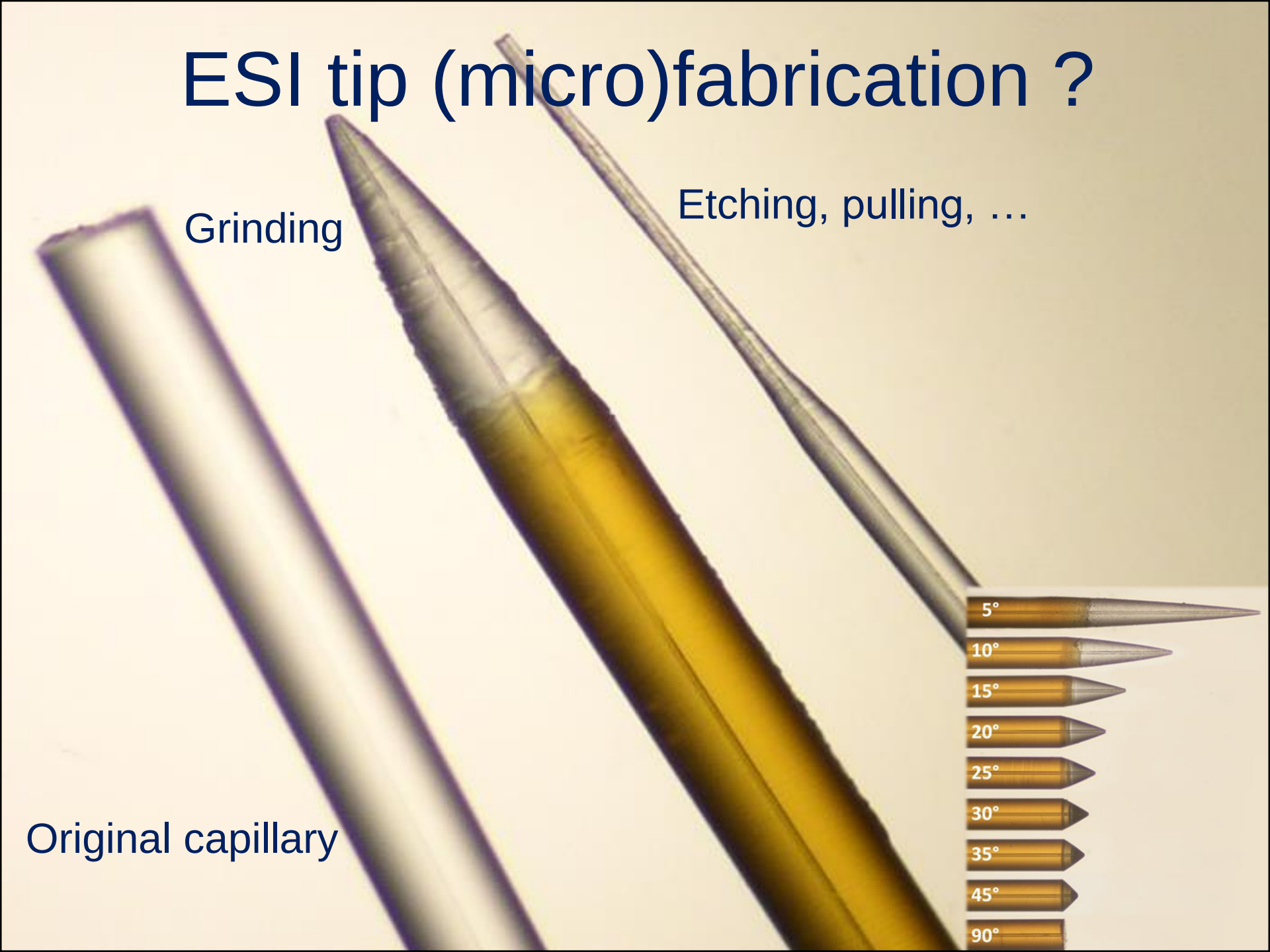
J. M. Ramsey, R. Ramsey Anal. Chem., 1997, 69, 1174-1178.

Electrospray

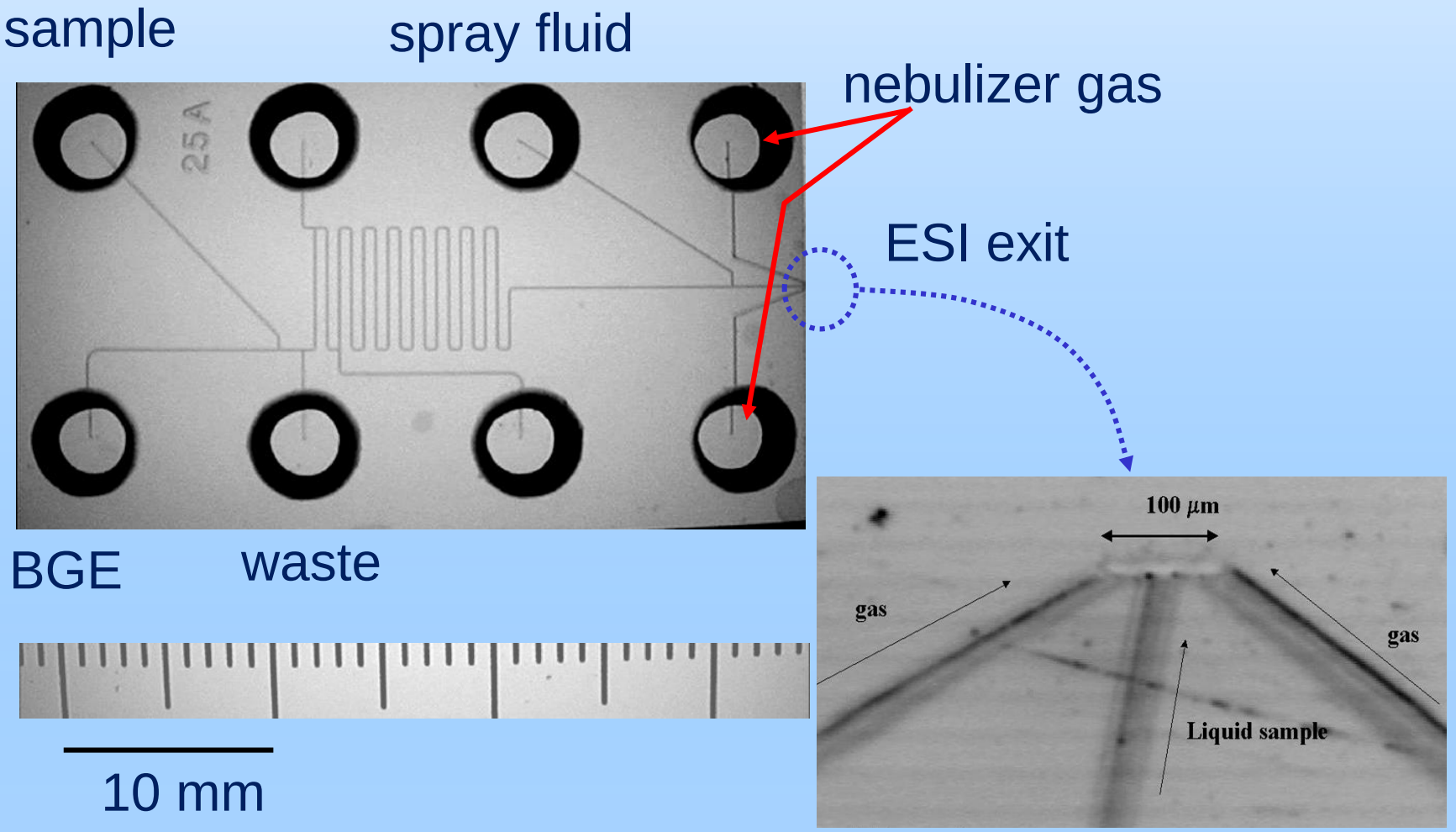
Flat surface - droplet

Capillary tip

ESI tip (micro)fabrication ?

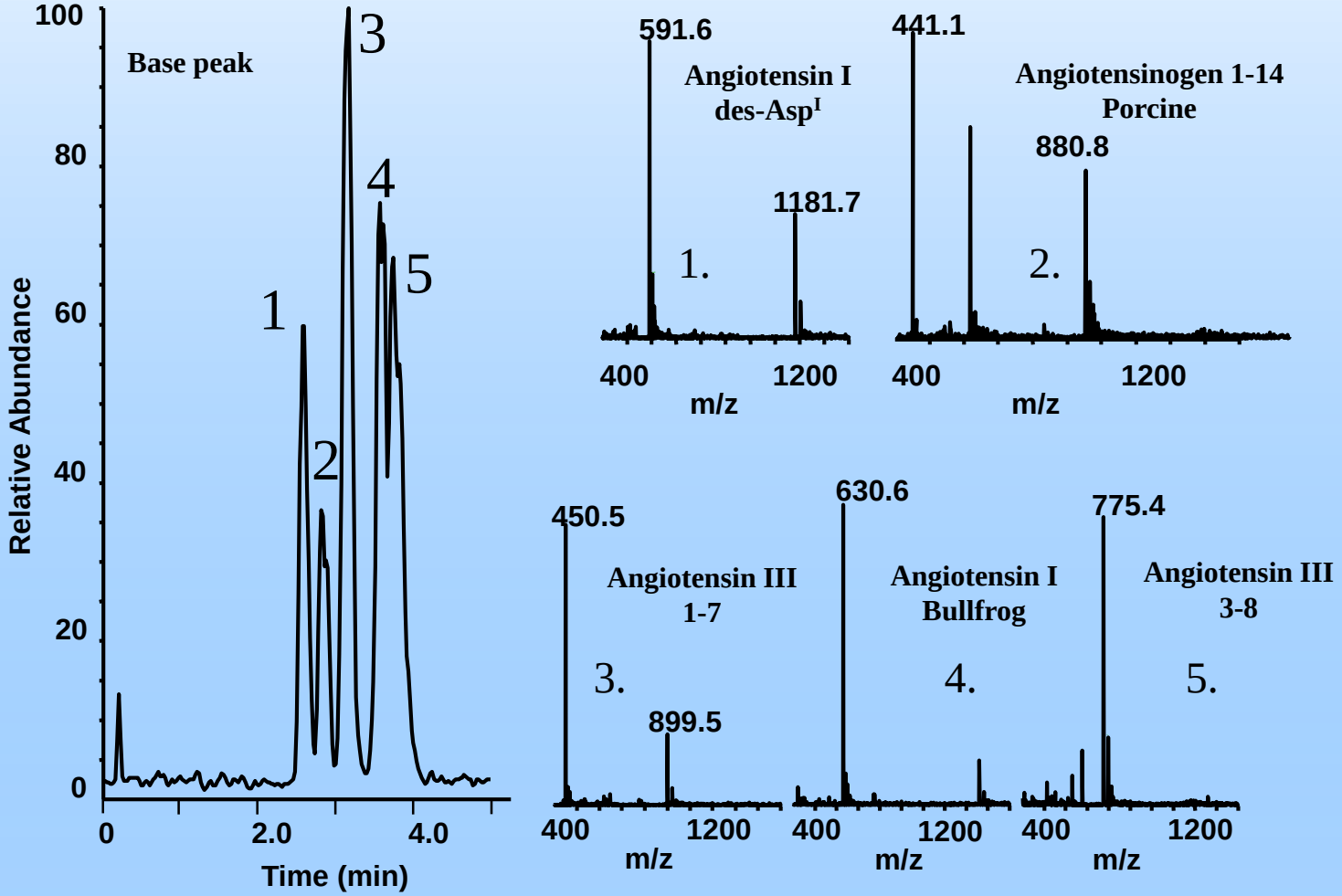


CE Microdevice with a Pneumatic Nebulizer



Zhang, B. Liu, H. Karger, B. L. Foret, F. *Anal. Chem.,* 1999, *71*, 3258-3264.

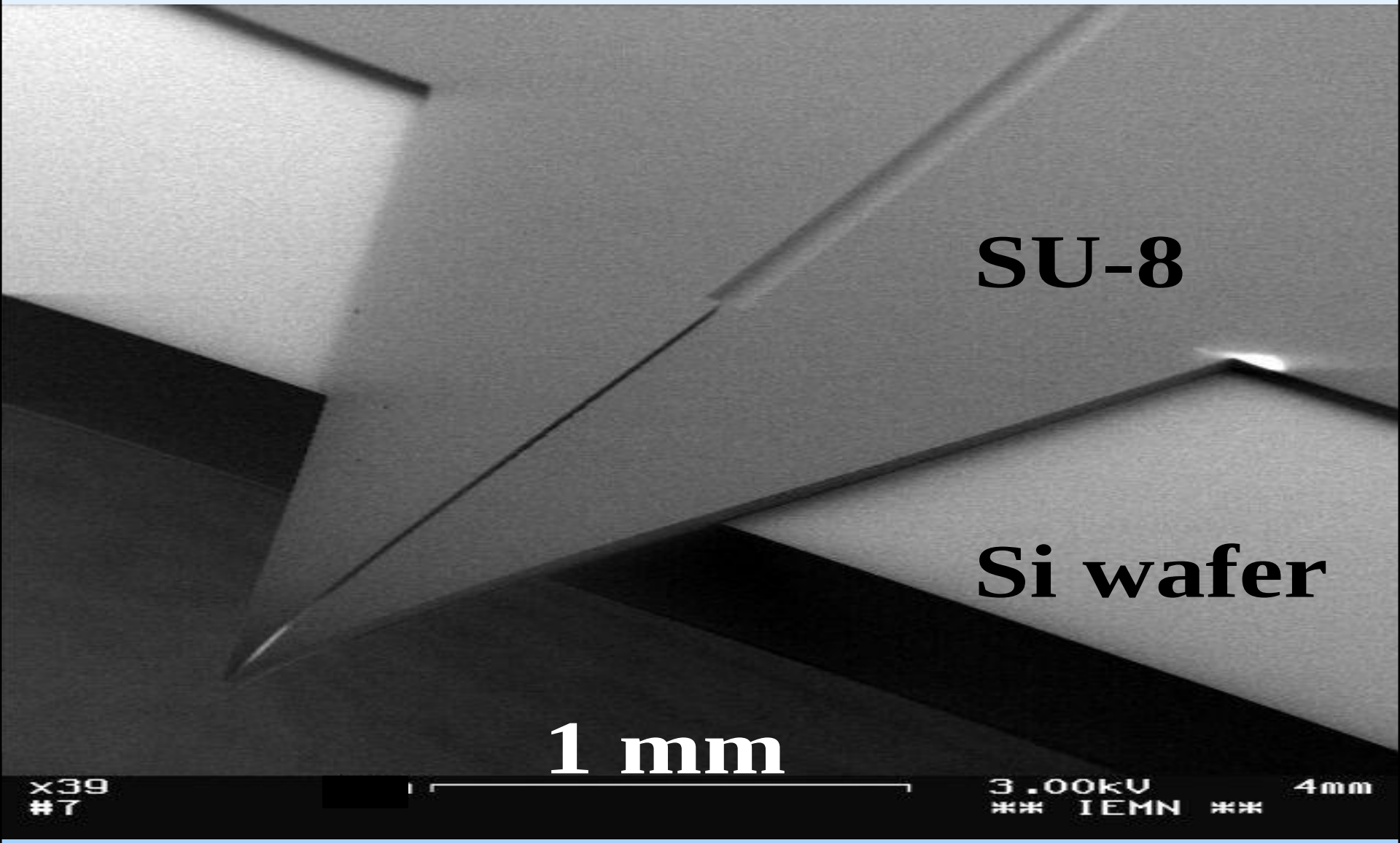
CE Microdevice with a Pneumatic Nebulizer



Zhang, B. Liu, H. Karger, B. L. Foret, F. *Anal. Chem.,* 1999, *71*, 3258-3264.

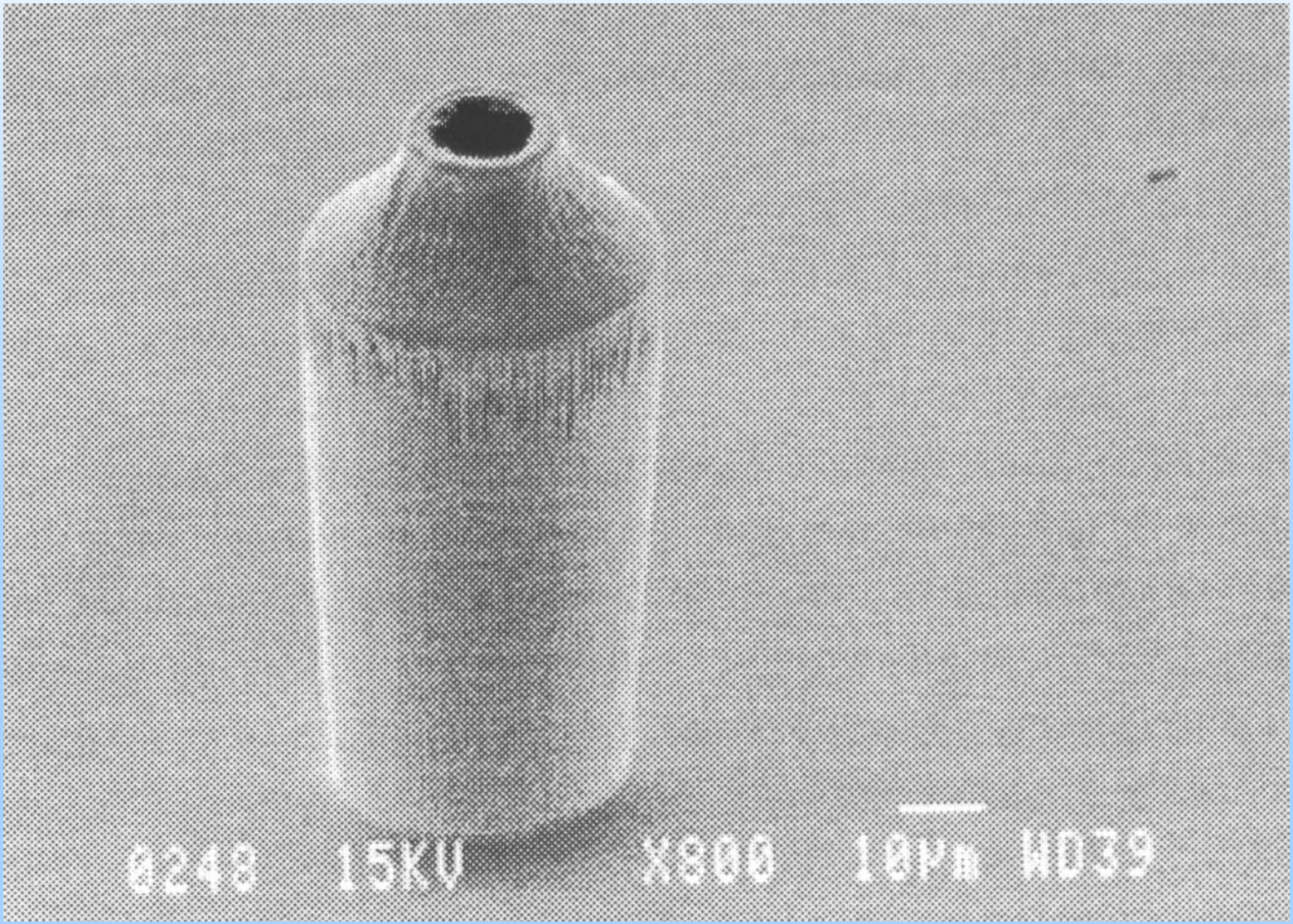
Micro-nib electrospray source

(SU-8 on a silicon wafer)



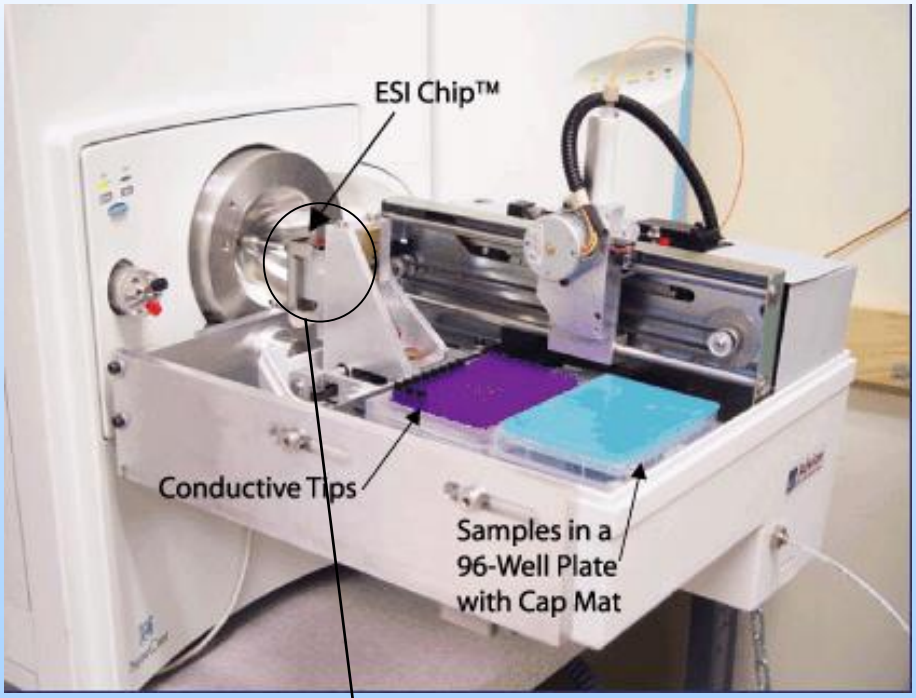
Le Gac S., Arscott S., Rolando C. ELECTROPHORESIS 2003 , 24, 3640-3647.

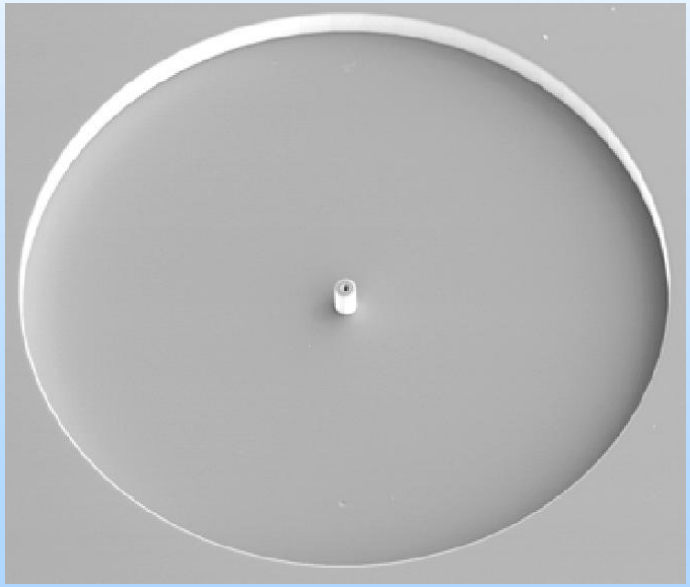
ESI tips produced by DRIE in silicon



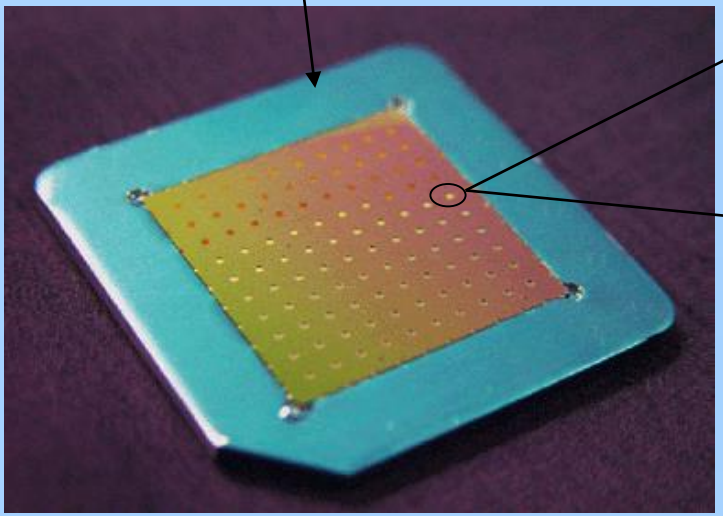
Sjödahl, J., Melin, J., Griss, P., Emmer, A., Stemme, G., Roeraade, J. Rapid Commun. Mass Spectrom. 2003, 17, 337—341.

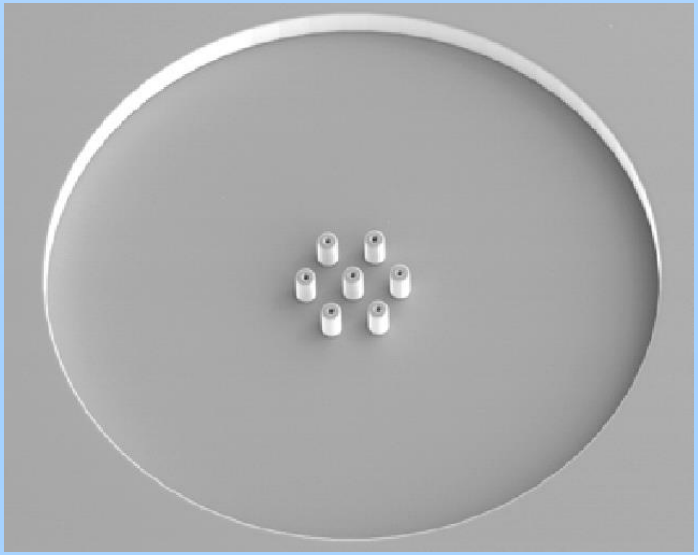
Infusion ESI Tip Array

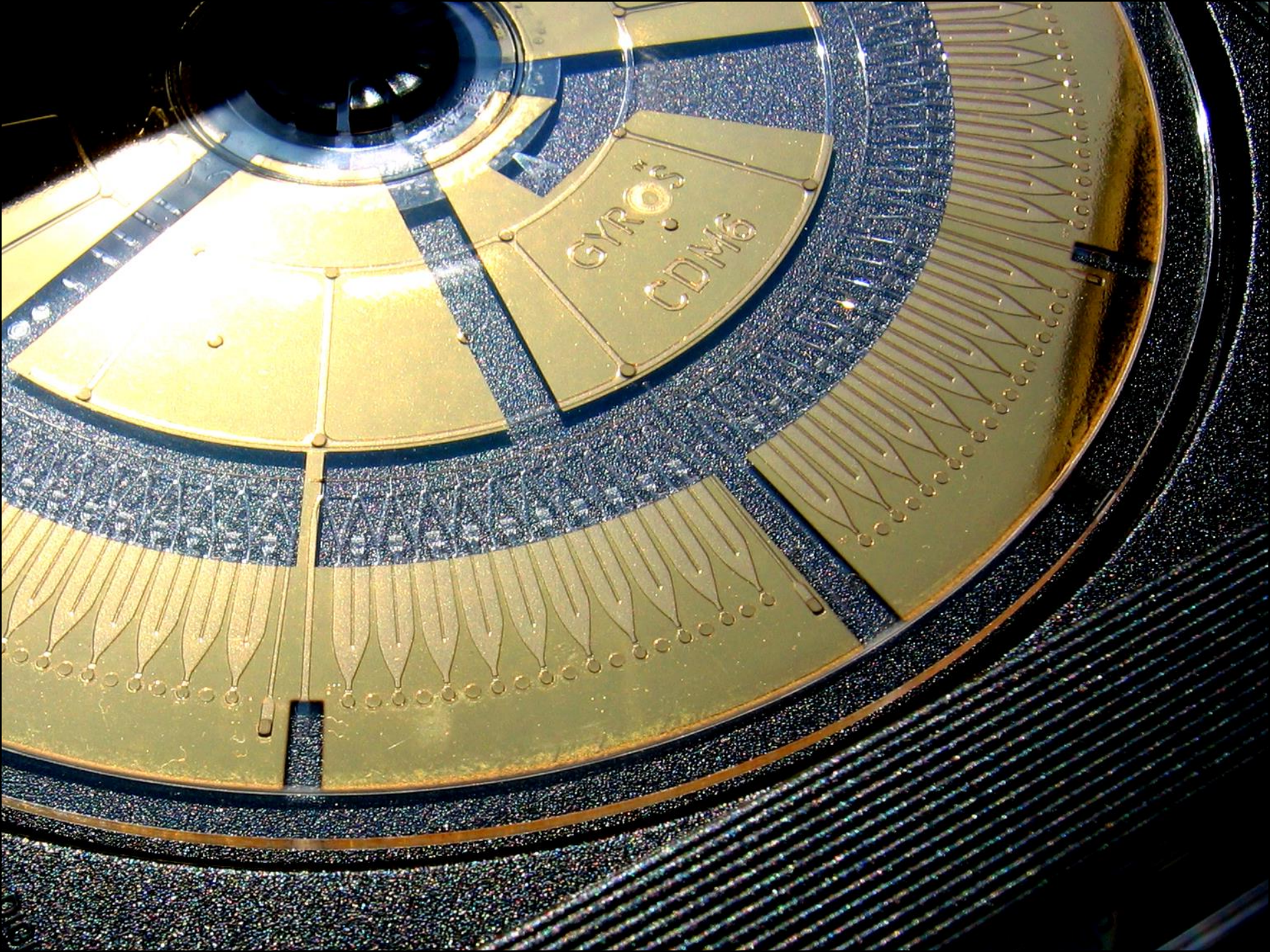




www.advion.com





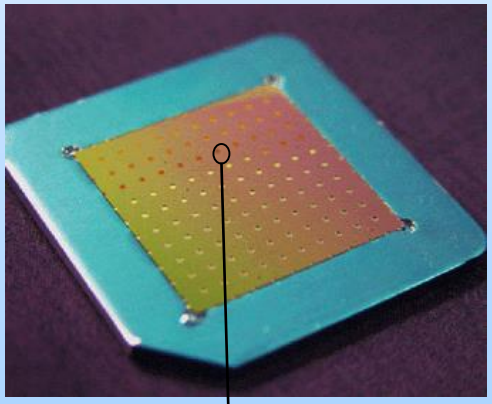

GYROS
CDM6

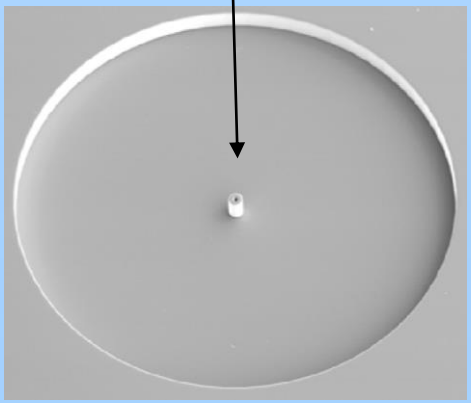
Integrated Au tips

100 mm

ESI tip fabrication

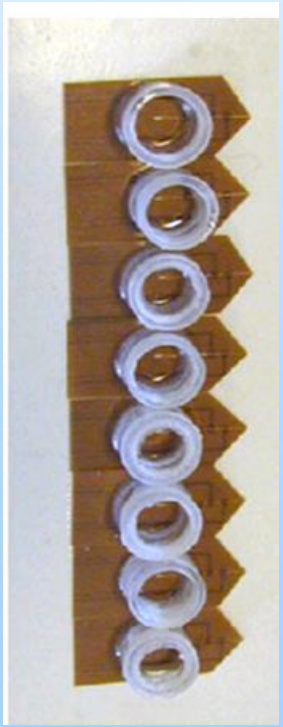
DRIE in silicone



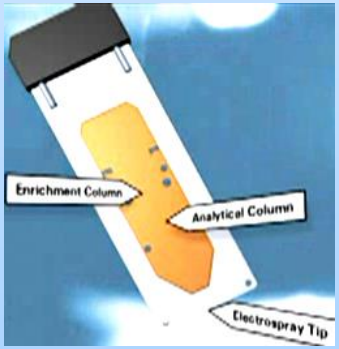


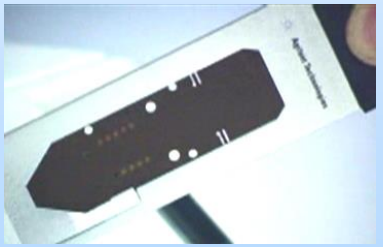
www.advion.com

Plasma etched in polyimide



www.diagnoswiss.com





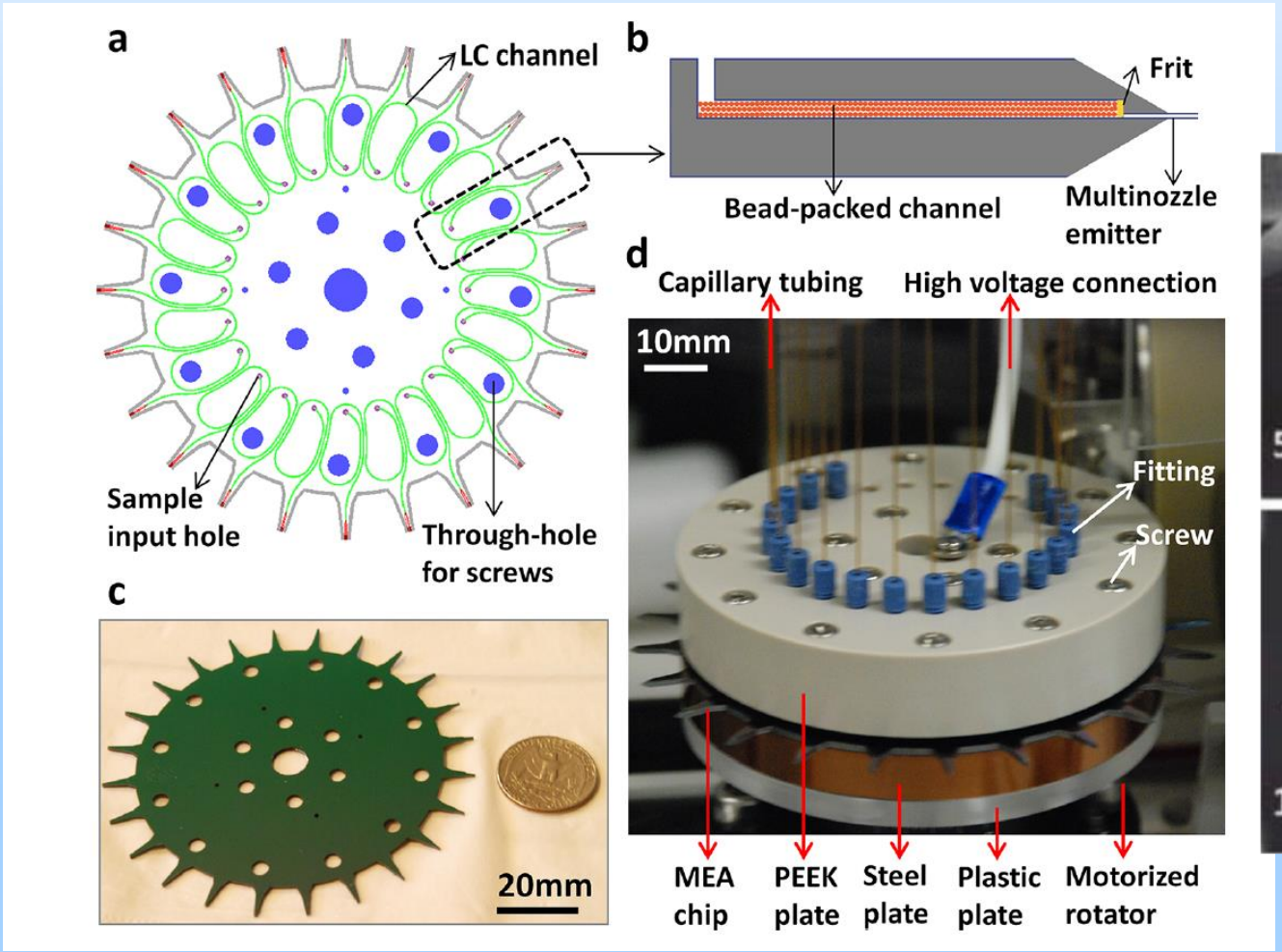
www.agilent.com

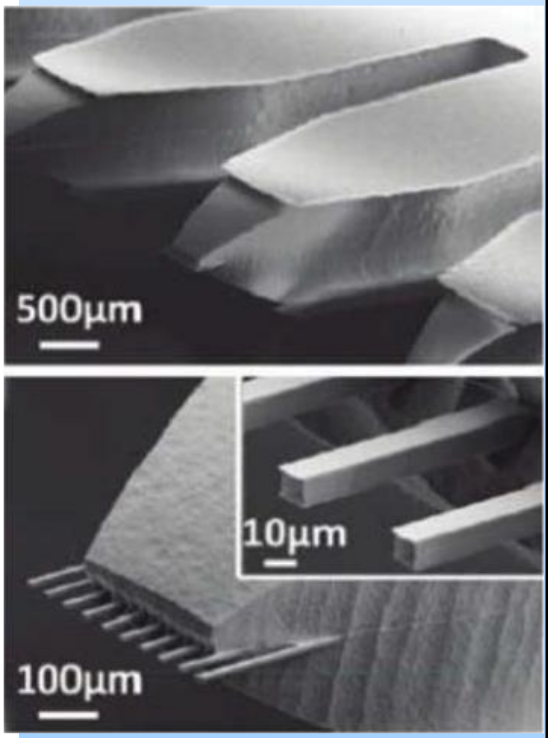
Injection molding in polypropylene

www.phoenix-st.com

Applications

Multinozzle Emitter Array Chips for Small-Volume Proteomics

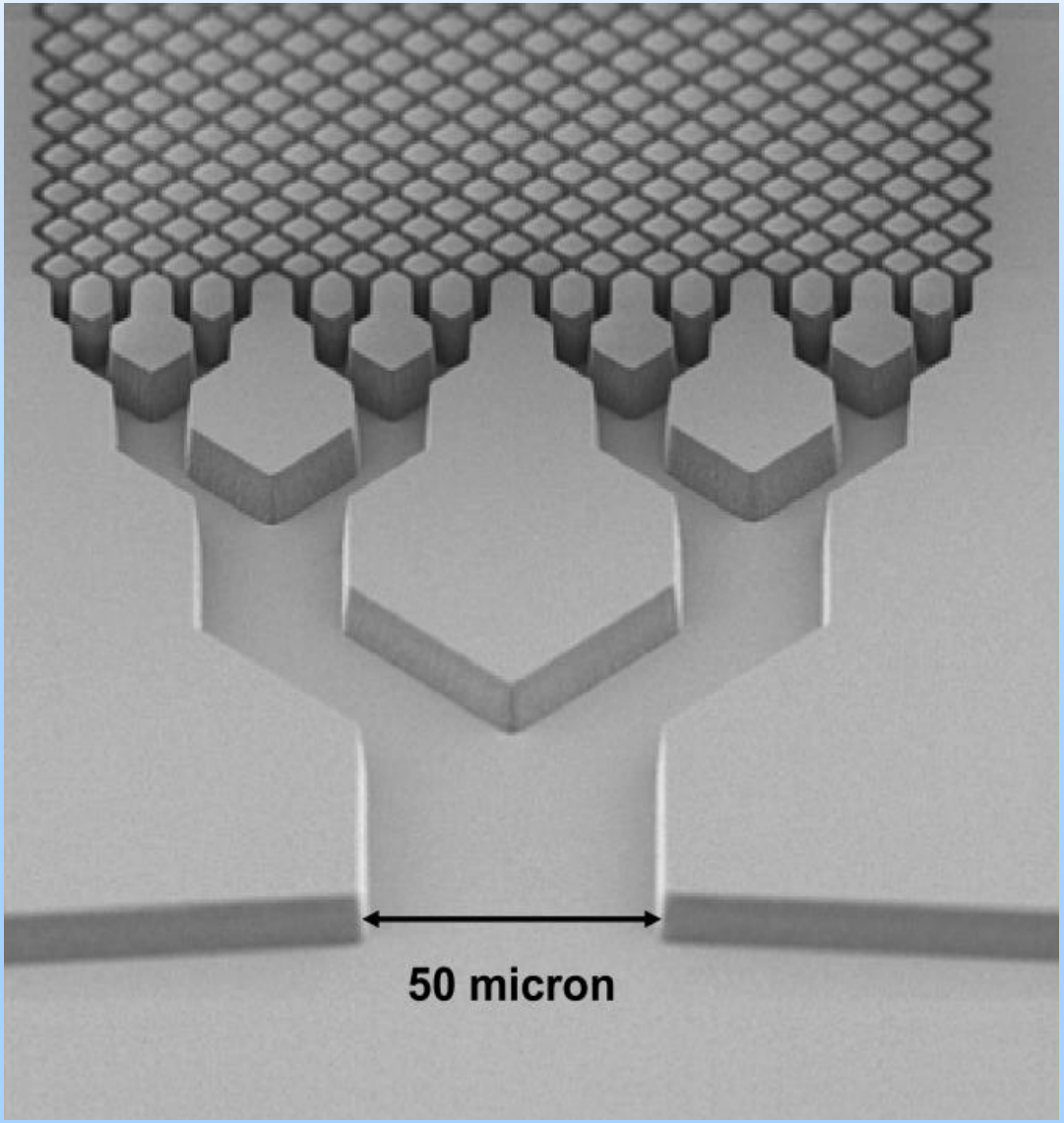


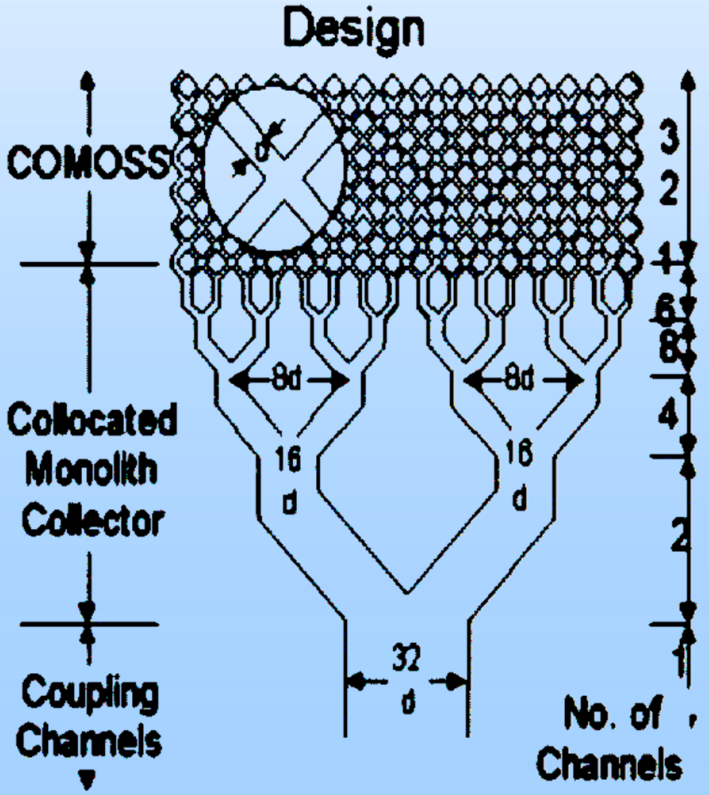


Mao, P; Gomez-Sjoberg, R; Wang, DJ. Anal. Chem. 2013, 85, 816-819.

Microfabricated Monolith Columns for Liquid Chromatography

Sculpting Supports for Liquid Chromatography

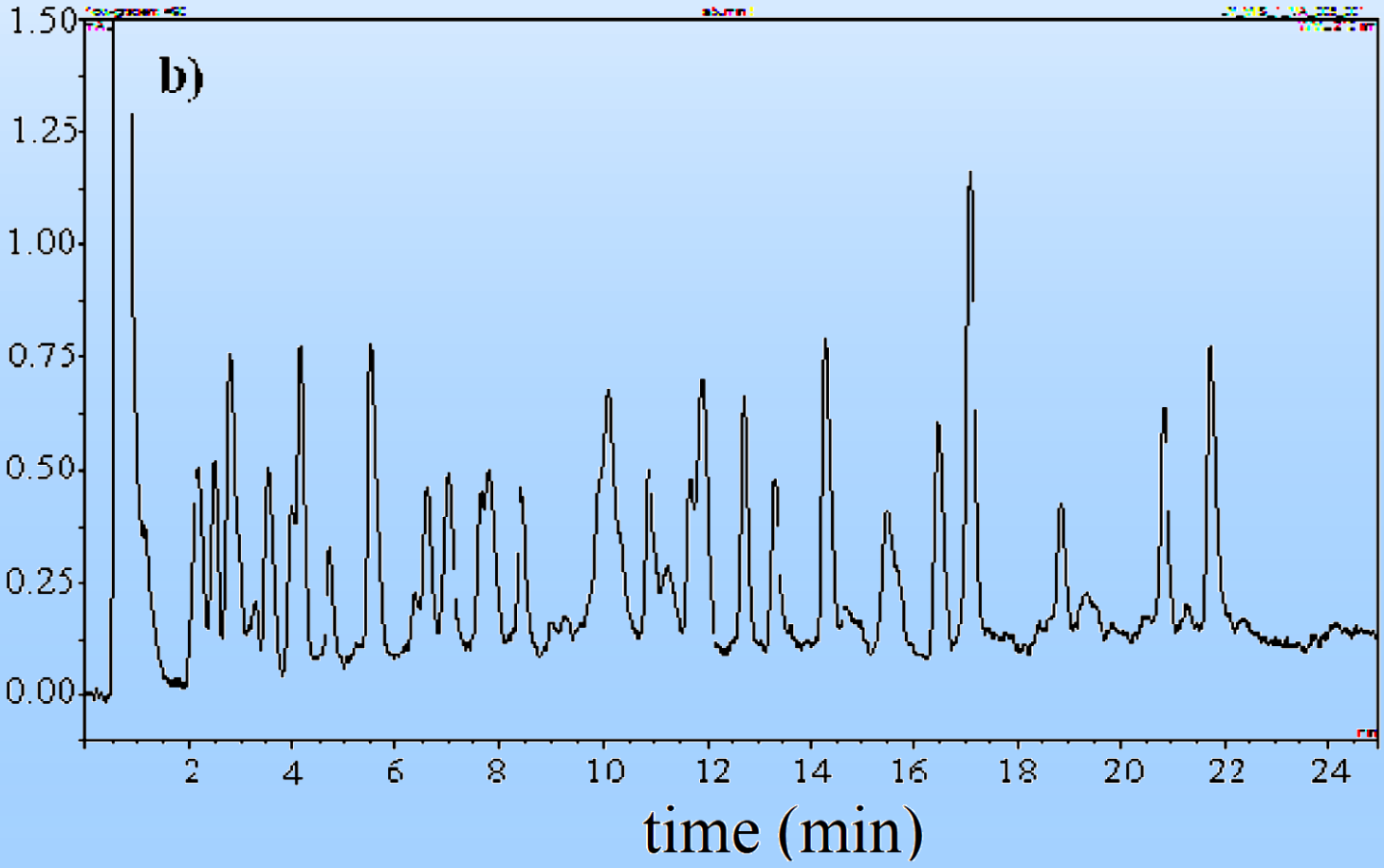




Fred E. Regnier J. High Resol. Chromatogr. **2000**, *23*, (1) 19–26

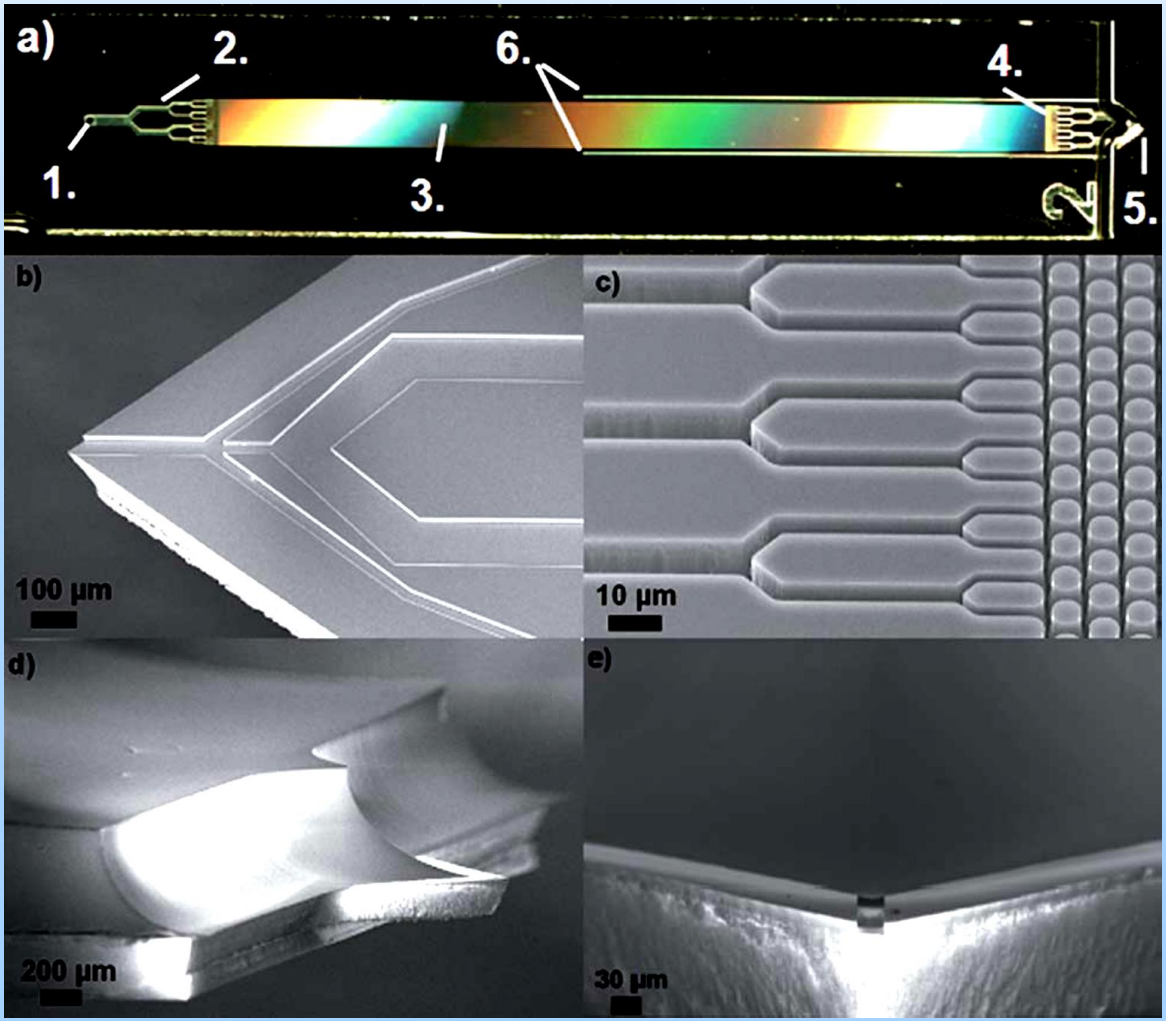
Gradient LC separation of albumin digest

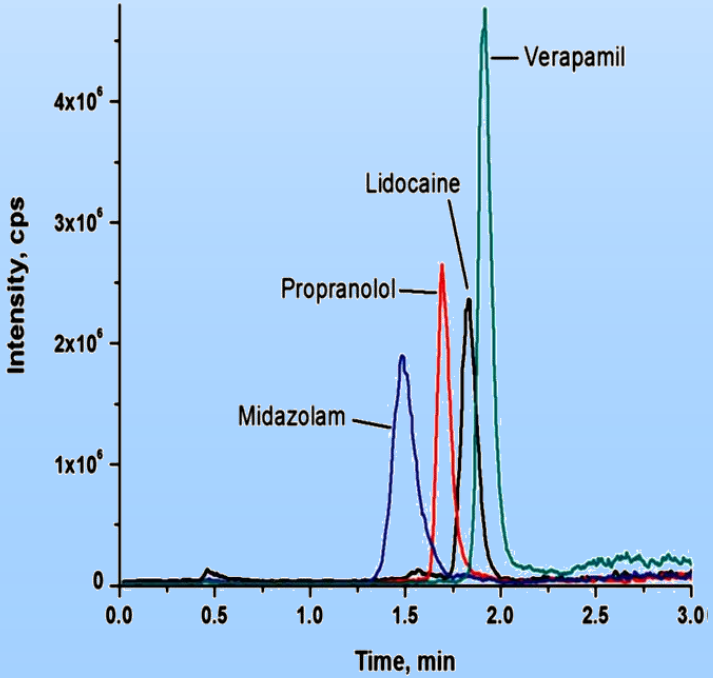
(4µl/min, 1 mg/ml, UV detection)



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

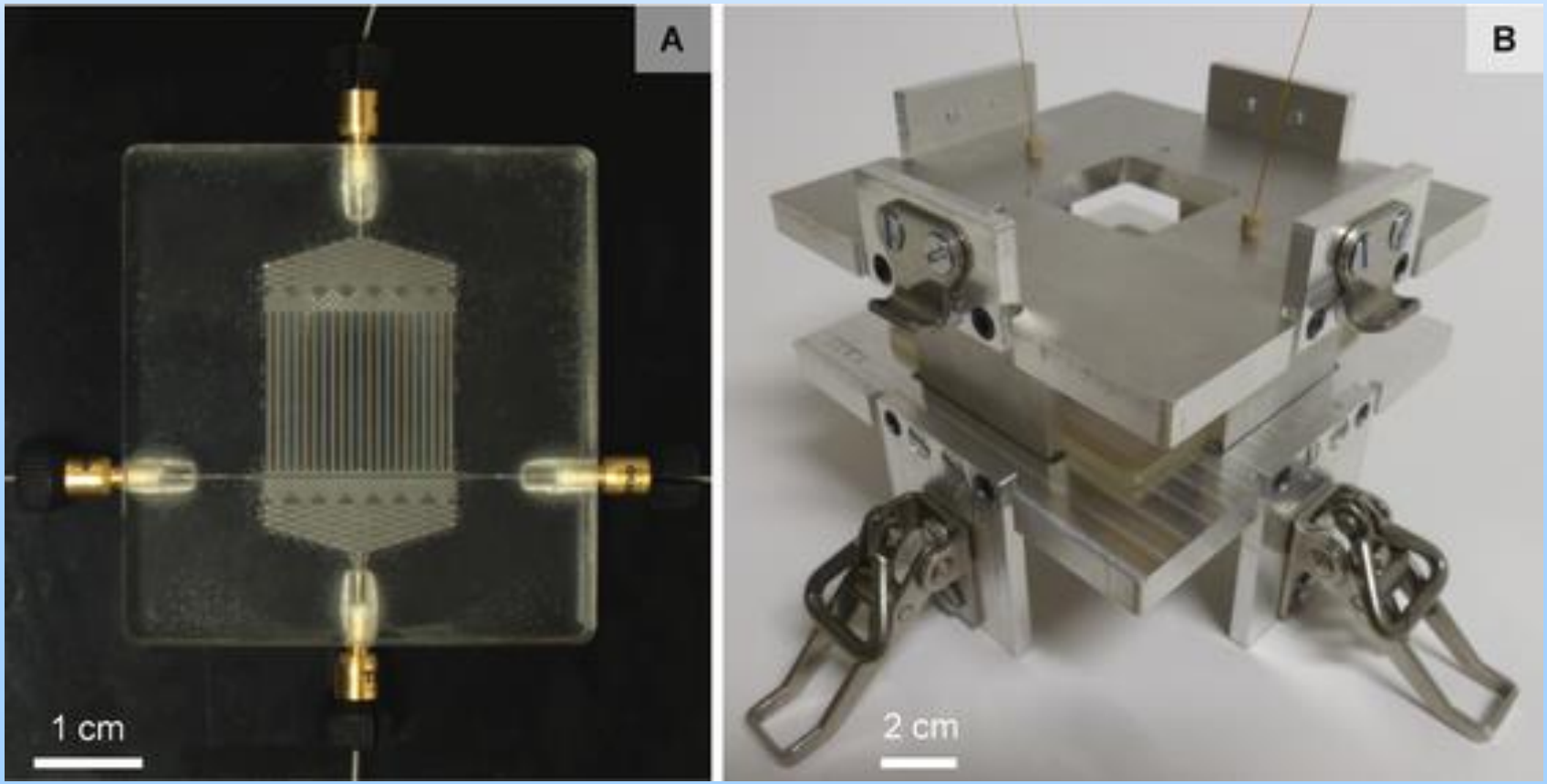
A microfabricated micropillar liquid chromatographic chip Monolithically integrated with an electrospray ionization tip





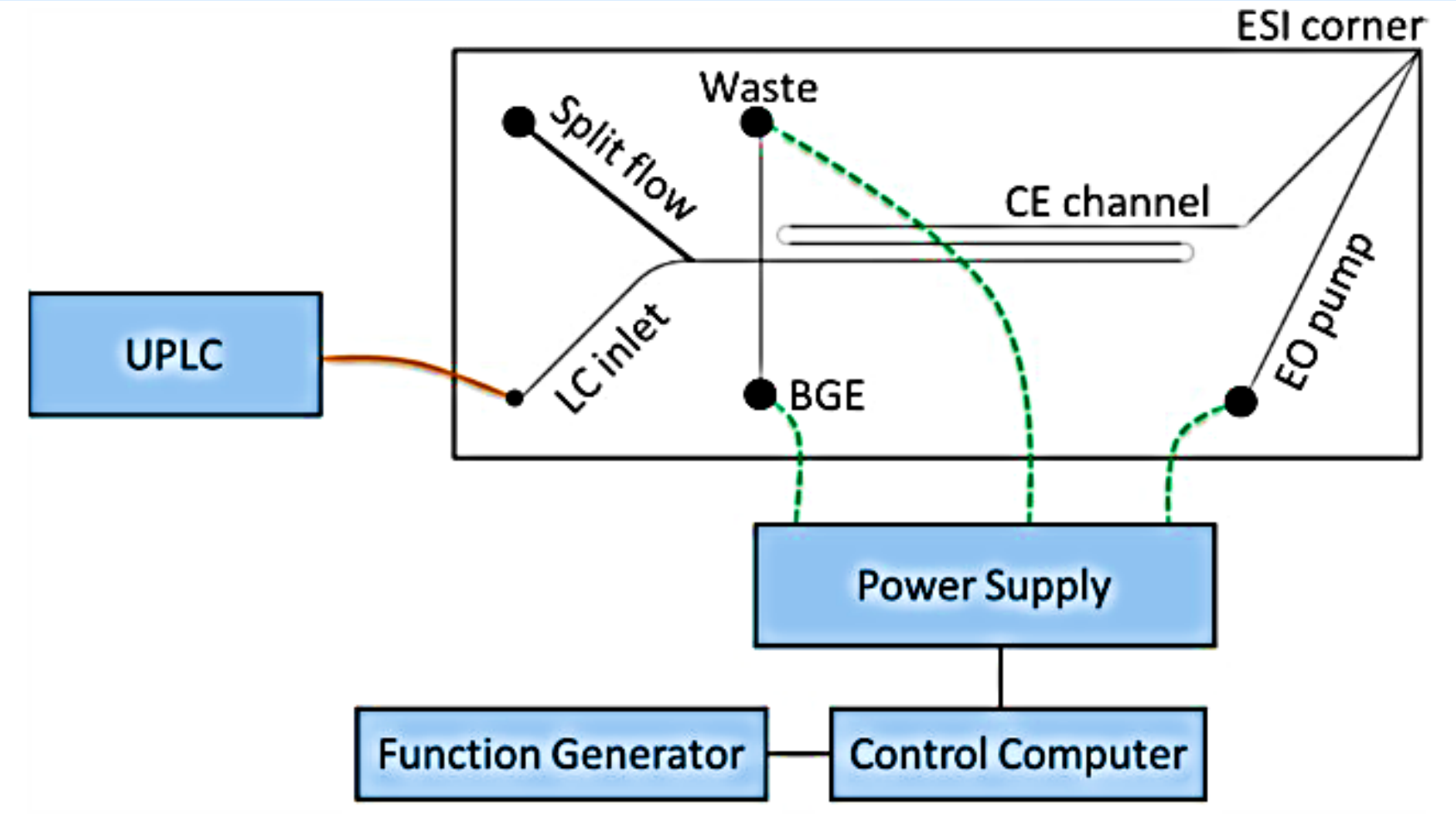
Lauri Sainiemi, Teemu Nissilä, Risto Kostiainen, Sami Franssila and Raimo A. Ketola
Lab Chip, 2012, 12, 325

Design of a microfluidic device for comprehensive spatial two-dimensional liquid chromatography



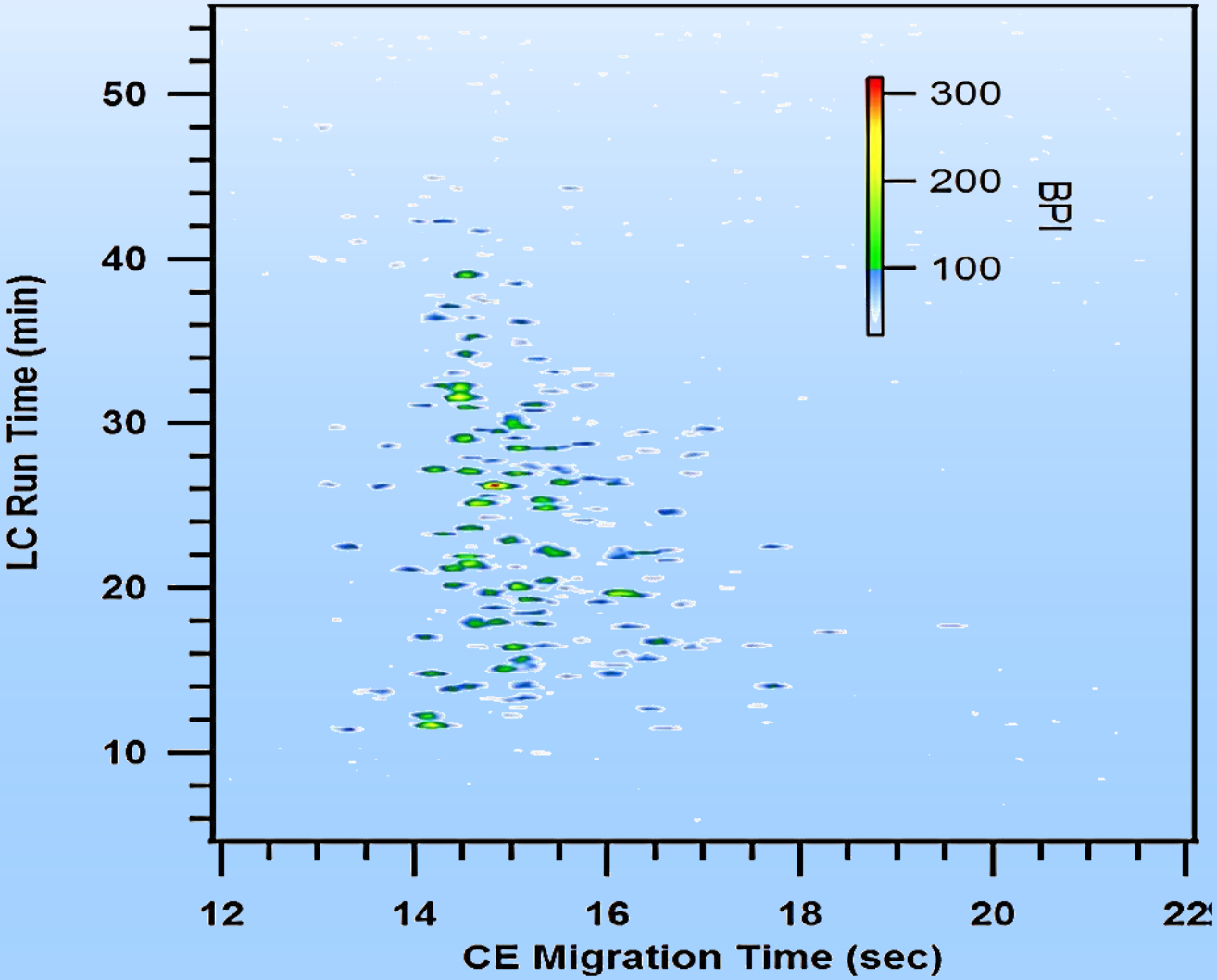
S. Eeltink, et al., J. Sep. Sci. 2015, 38,1123-1129.

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



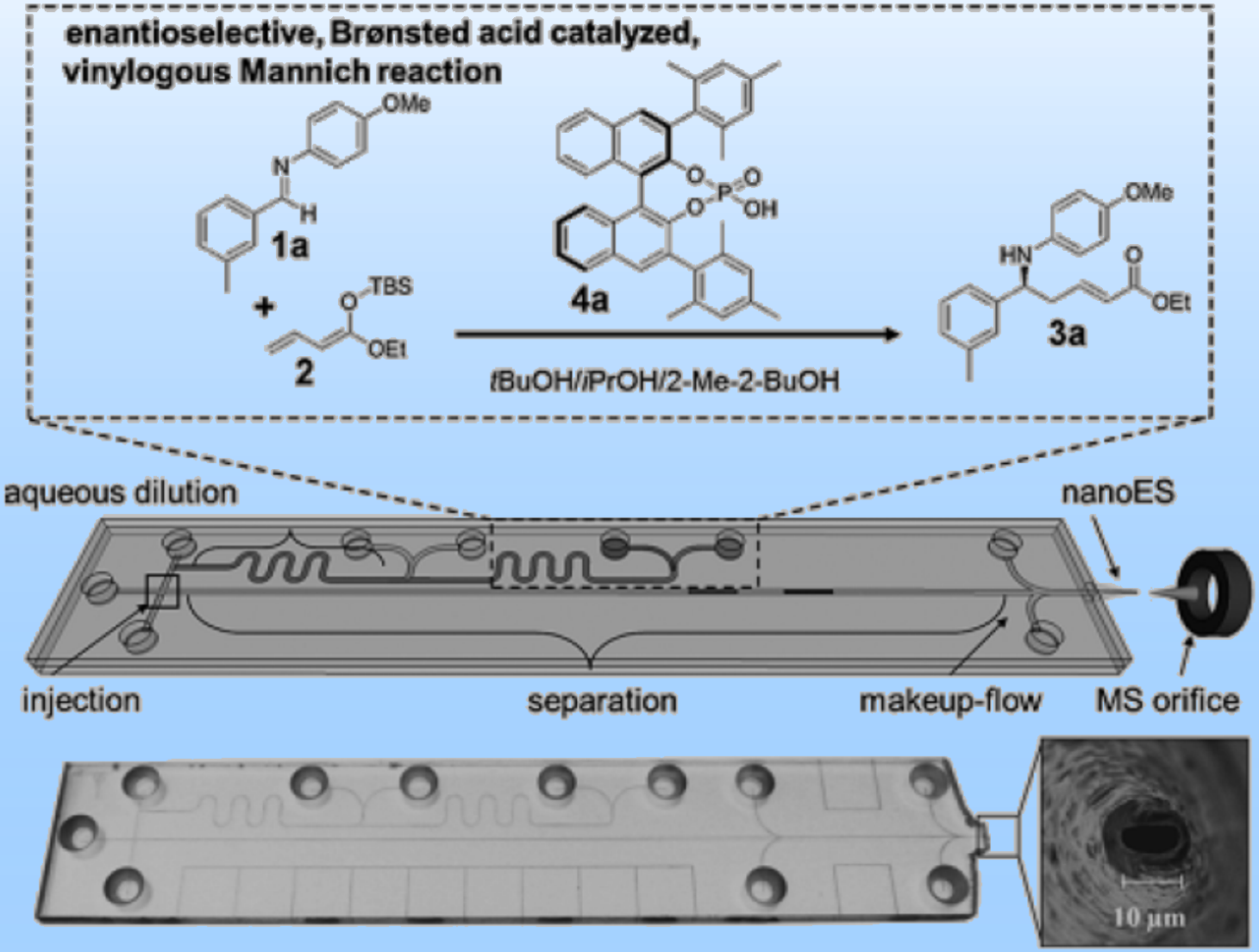
Mellors, JS; Black, WA; Chambers, AG; Starkey, JA; Lacher, NA; Ramsey, JM. Anal. Chem. 2013, 85, 4100-4106

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



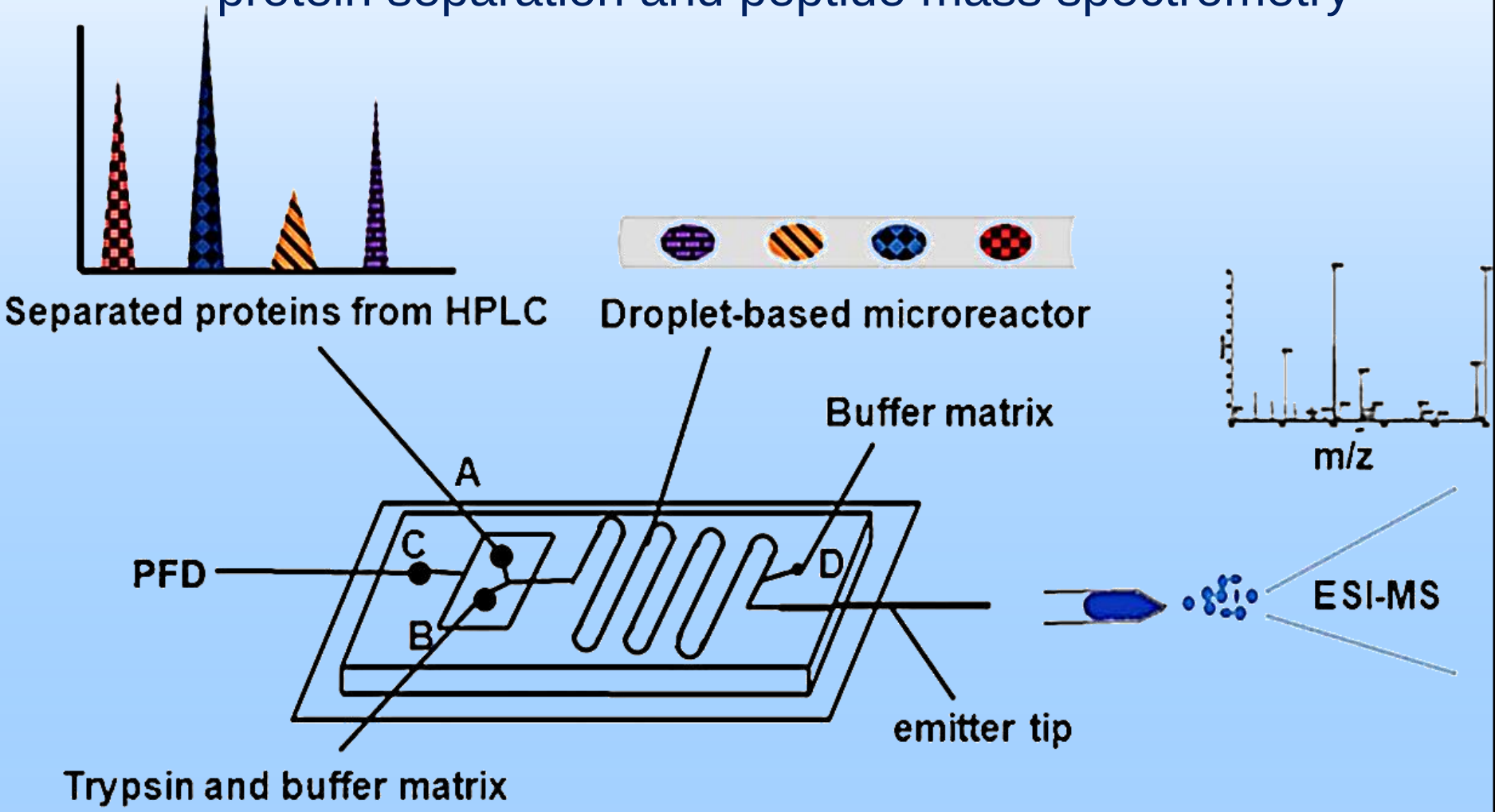
Mellors, JS; Black, WA; Chambers, AG; Starkey, JA; Lacher, NA; Ramsey, JM. Anal. Chem. 2013, 85, 4100-4106

Asymmetric Organocatalysis and Analysis on a Nanospray Chip



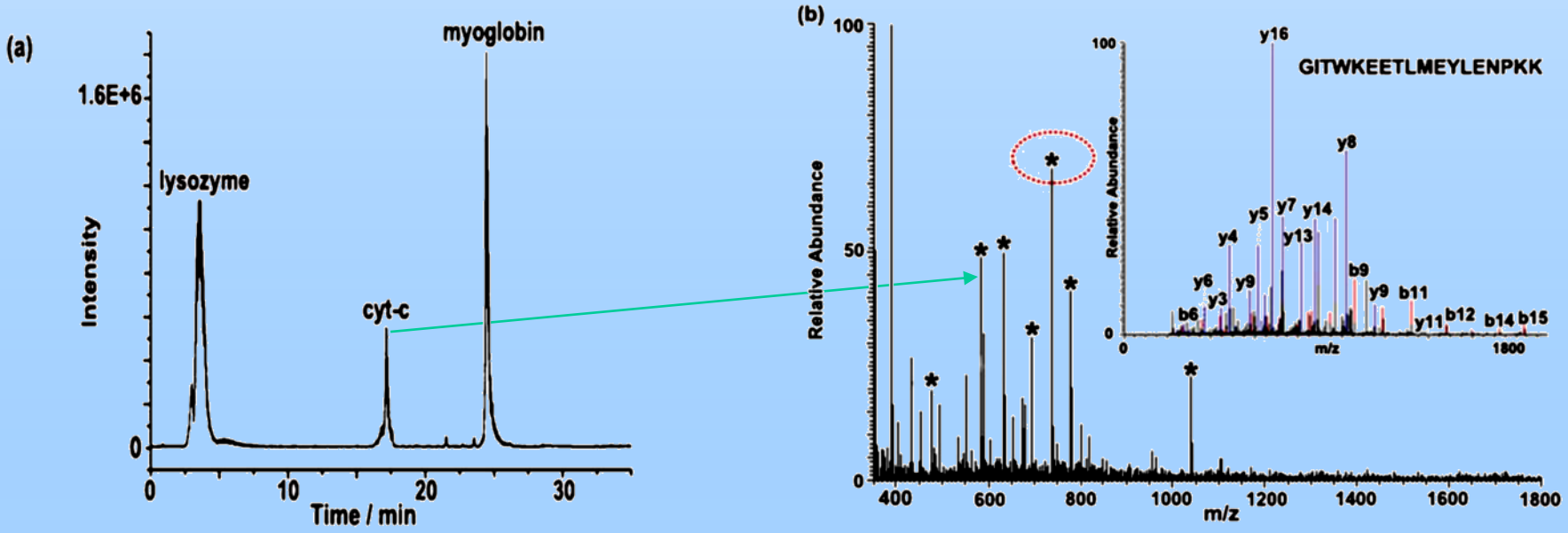
S. Fritzsche, S. Ohla, P. Glaser, D. S. Giera, M. Sickert, C. Schneider and D. Belder
Angew. Chem., Int. Ed., 2011, 50, 9467-9470.

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.

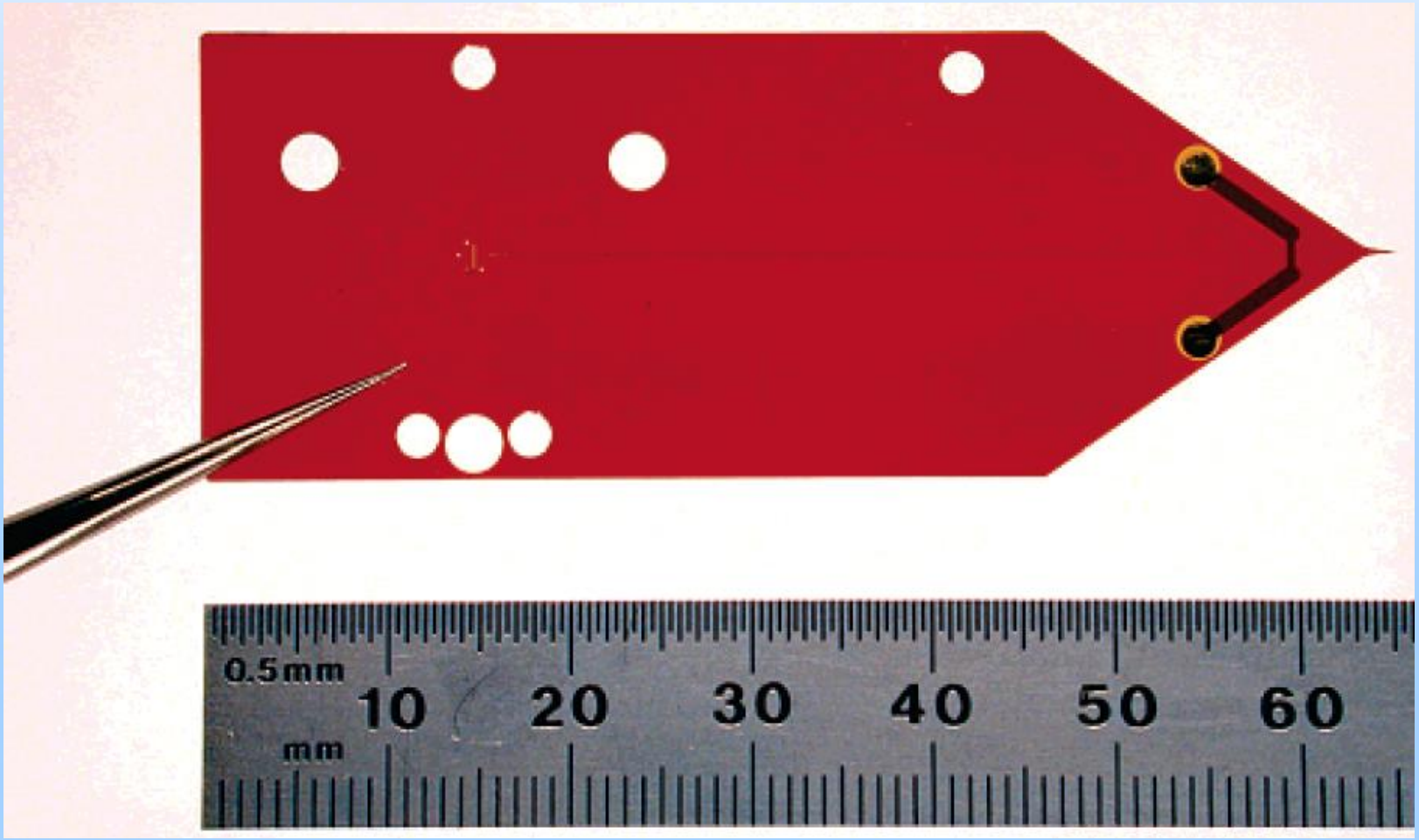
Proteolysis in microfluidic droplets: an approach to interface protein separation and peptide mass spectrometry



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

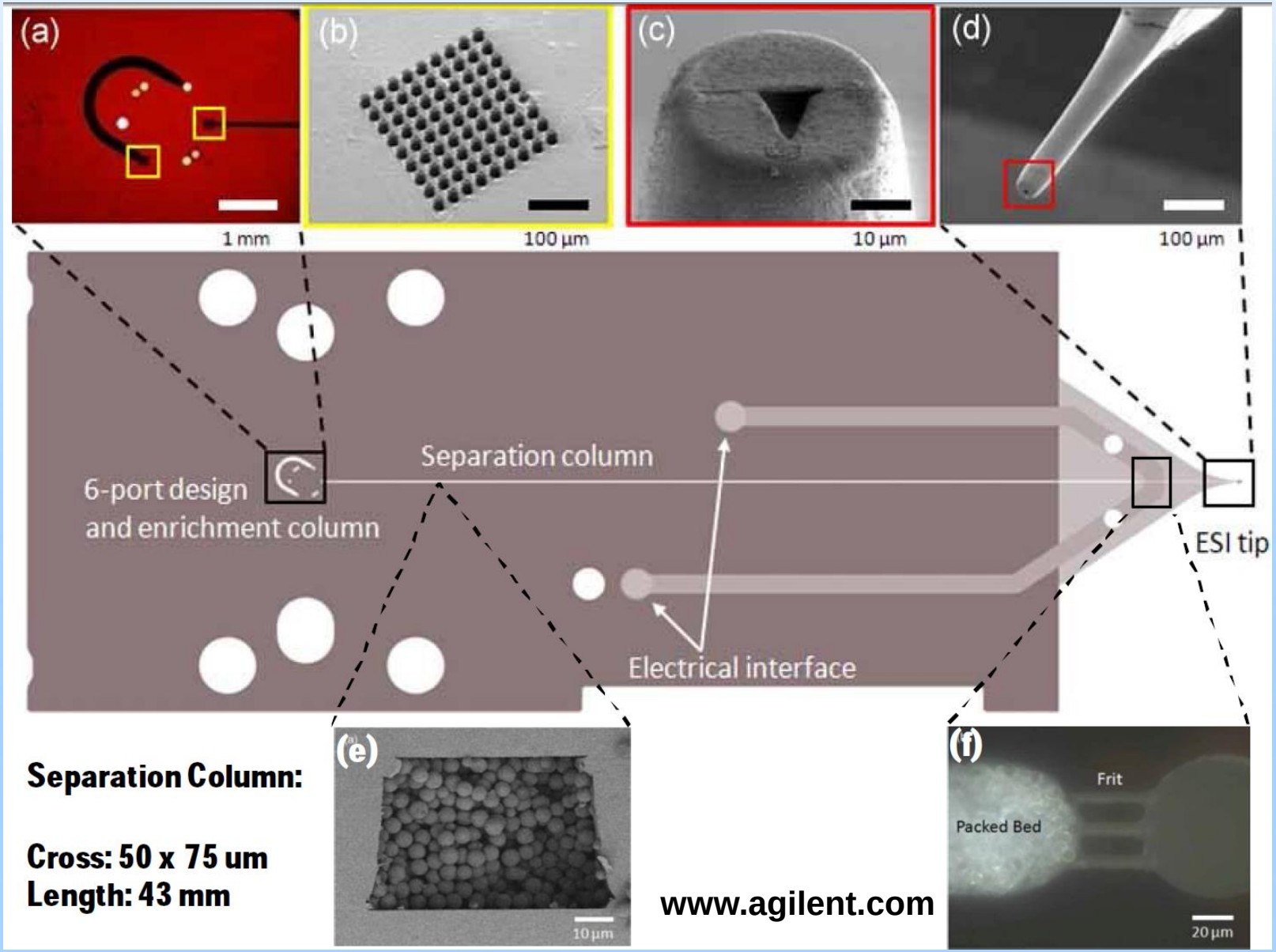
Commercialization

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

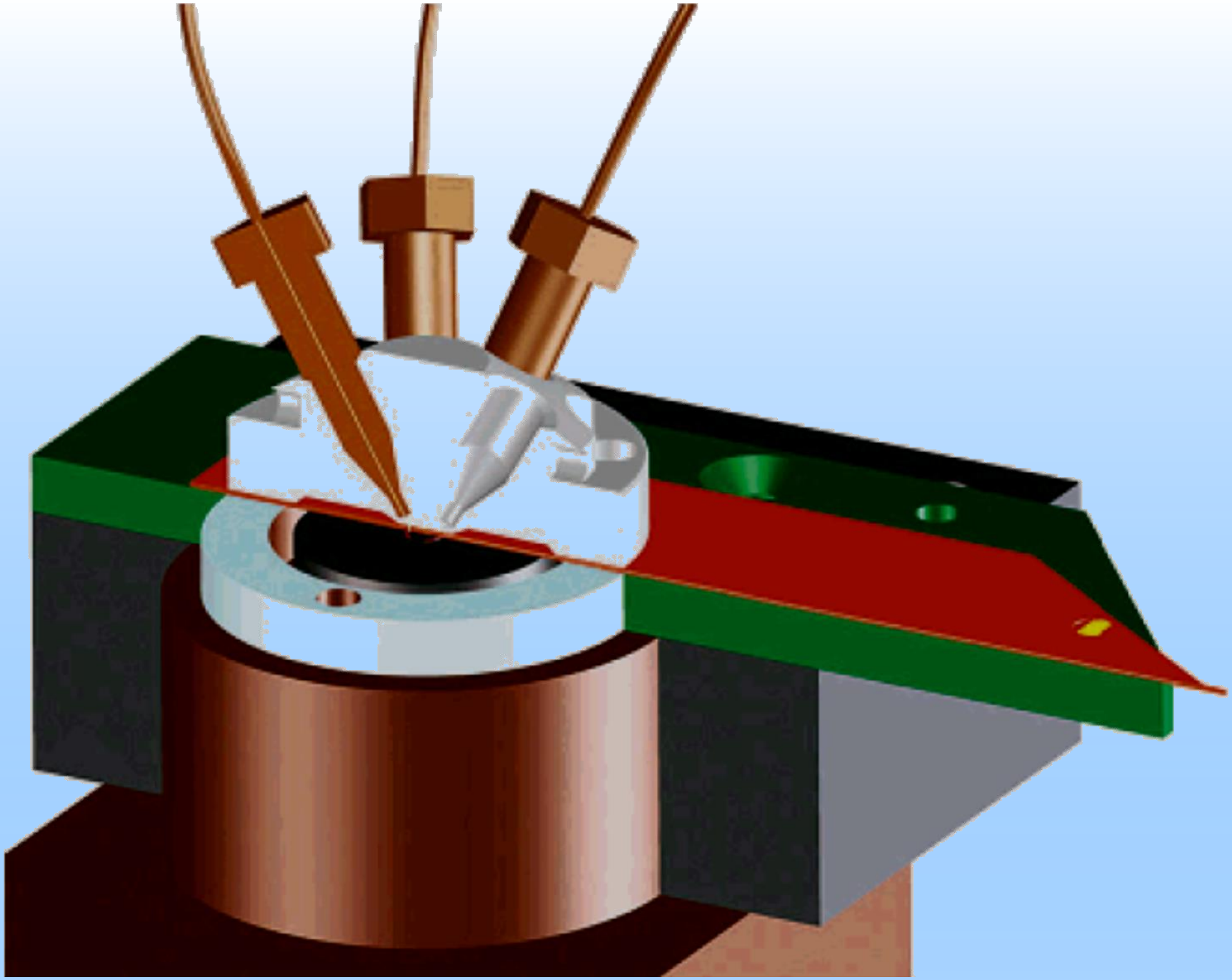
Polyimide HPLC-chip, integrating an enrichment column, frits, a laser ablated ESI tip and trapazoidal separation column



Separation Column:

Cross: 50 x 75 um
Length: 43 mm

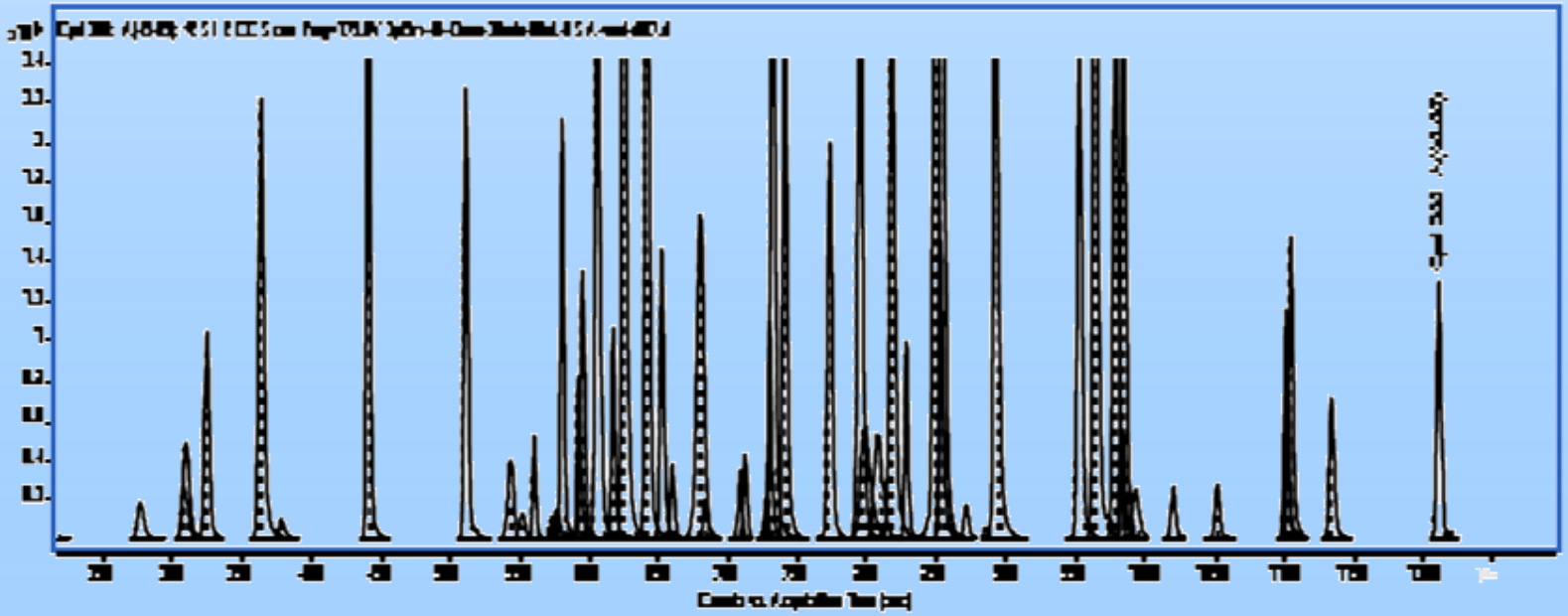
www.agilent.com



Segmented column HPLC/chip

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

Multi-segment three chip stack in enclosure.

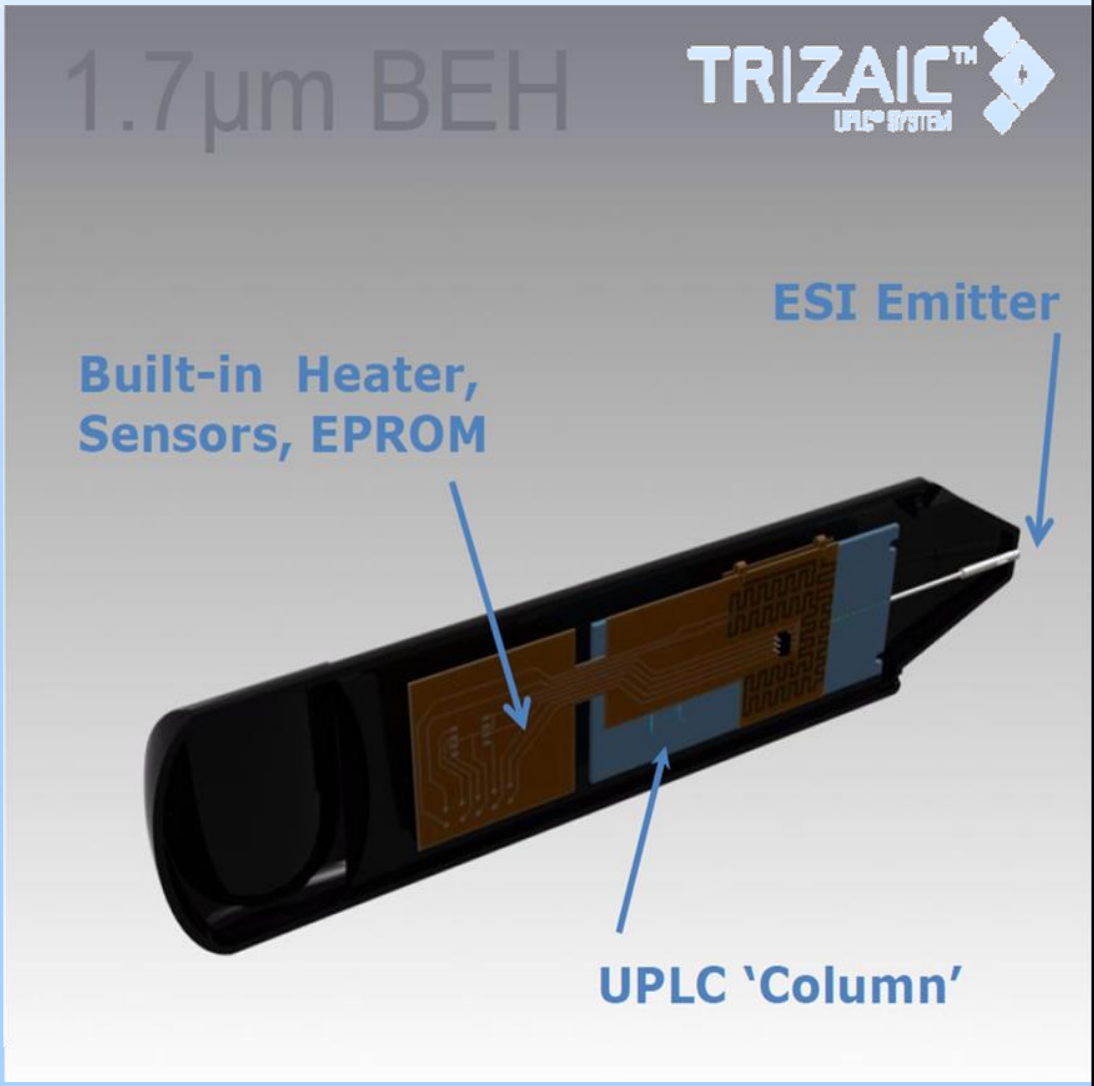


BSA digest separated with a 30min gradient on a 2 column segmented chip, packed with 3.5µm particles

www.agilent.com

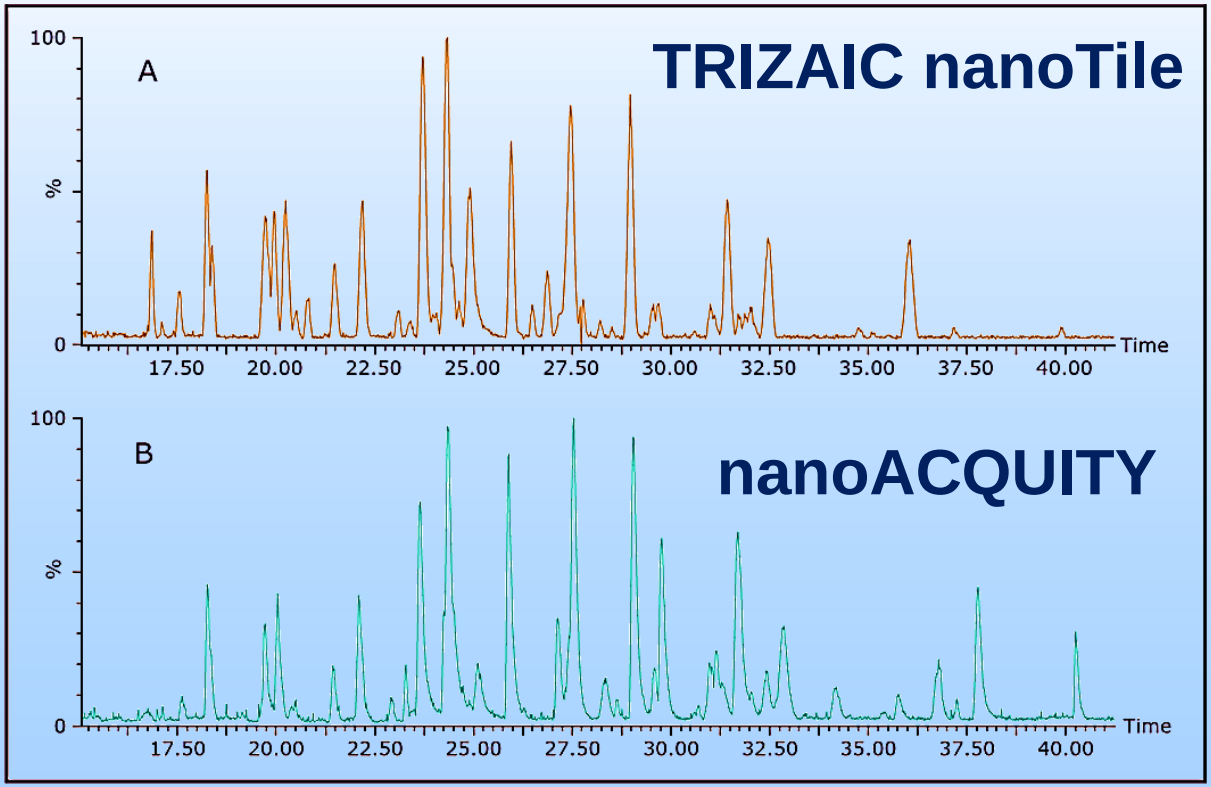
TRIZAIC nanoTile - Waters

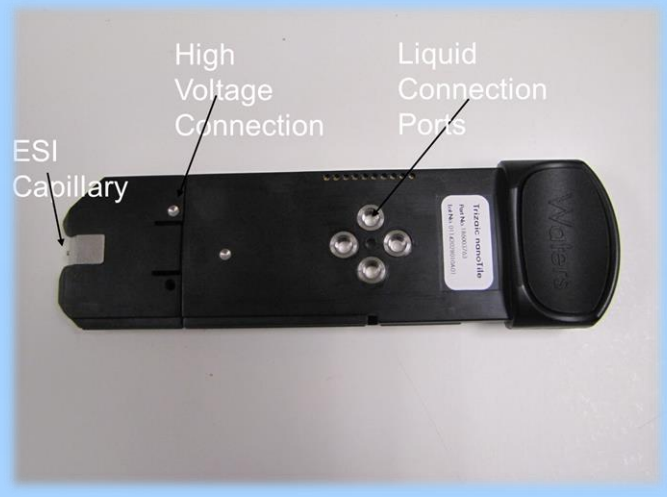
- UPLC Performance
- All fluidic connections are pre-made & factory tested
- Integrated ESI Emitter
- Low System Volumes
- Decreased Band Broadening
- Higher Sensitivity
- Incorporates:
  - Heater & Sensor
  - EPROM
- Increased Reproducibility



Enolase digest

70 fmol, 2 μm particles





- 150 µm ID Channel
- Sub-2-µm UPLC® Chemistries
- 10,000 psi Pressure Capability
- 1–7 pH Range
- Plug and Play Design
- Built-in eCord™
- Built-in Emitter
- Embedded Column Heater

Green tape

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

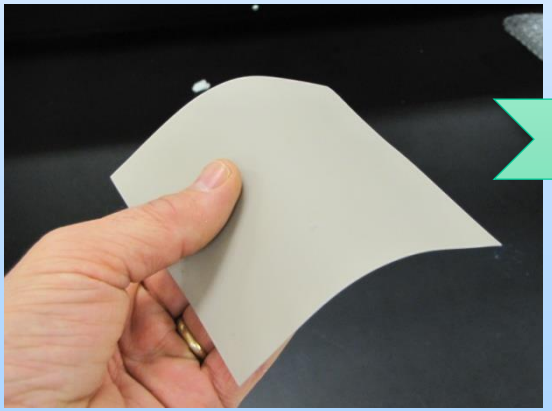
Product Description
951 Green Tape is a low-temperature cofired ceramic tape.
The 951 system comprises a complete cofireable family of Au and Ag metallizations, buried passives, and encapsulants.
951 is available in multiple thicknesses for use as an insulating layer in:

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

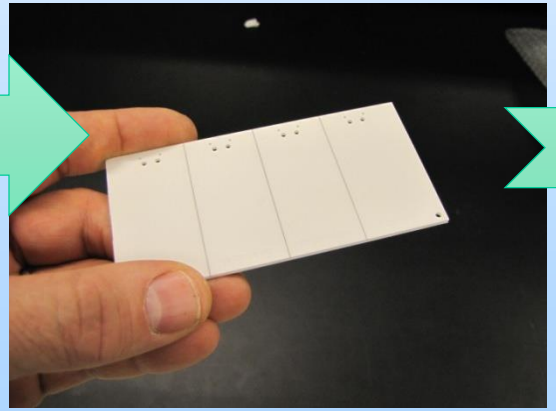
http://www.dupont.com/mcm

Ceramic Microfluidic Fabrication

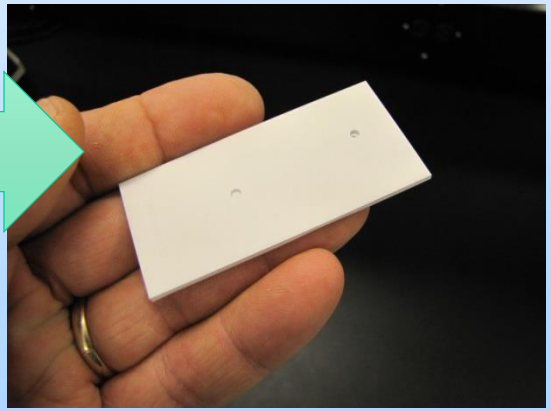
Cut Ceramic Material

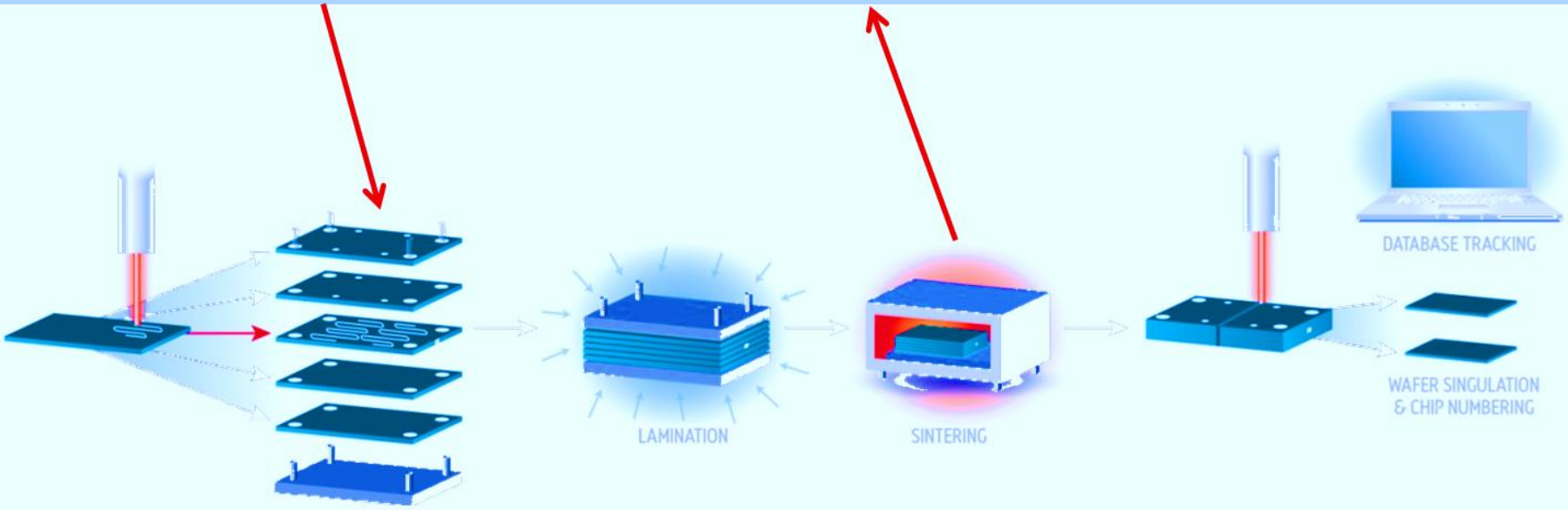


Fired Wafer

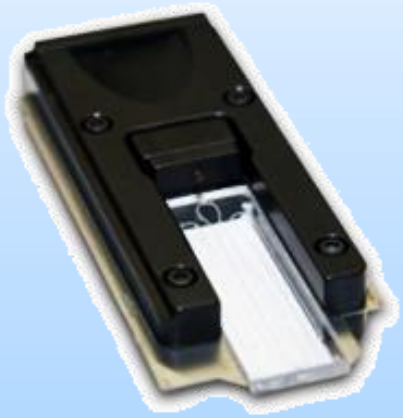


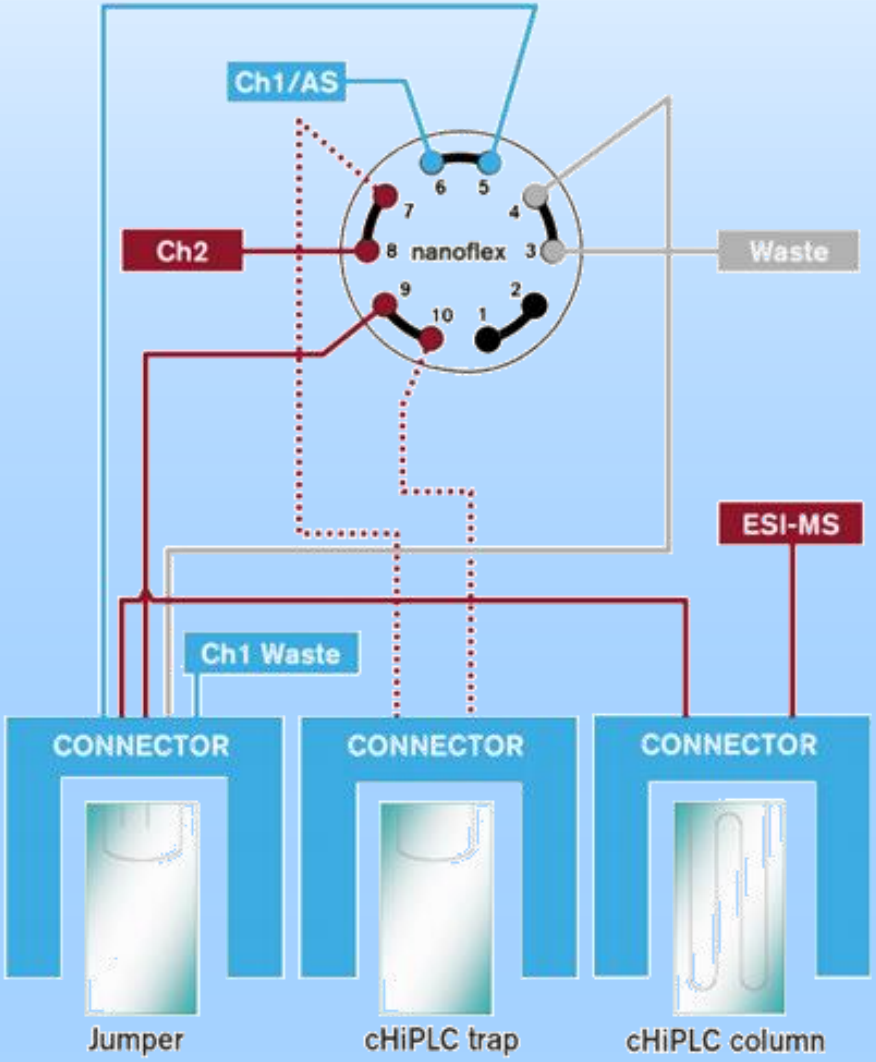
Final Diced Part



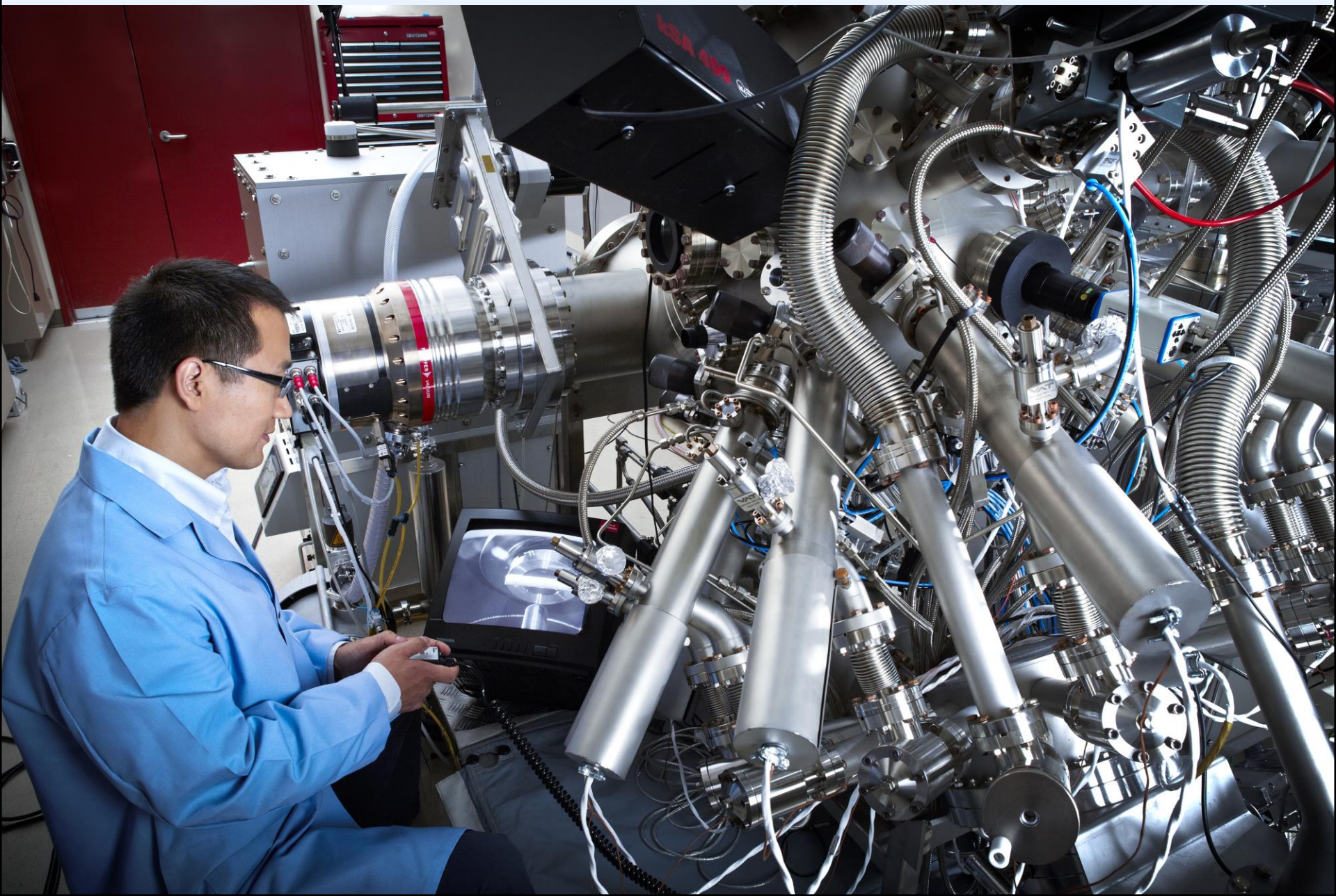


Packed glass LC chip





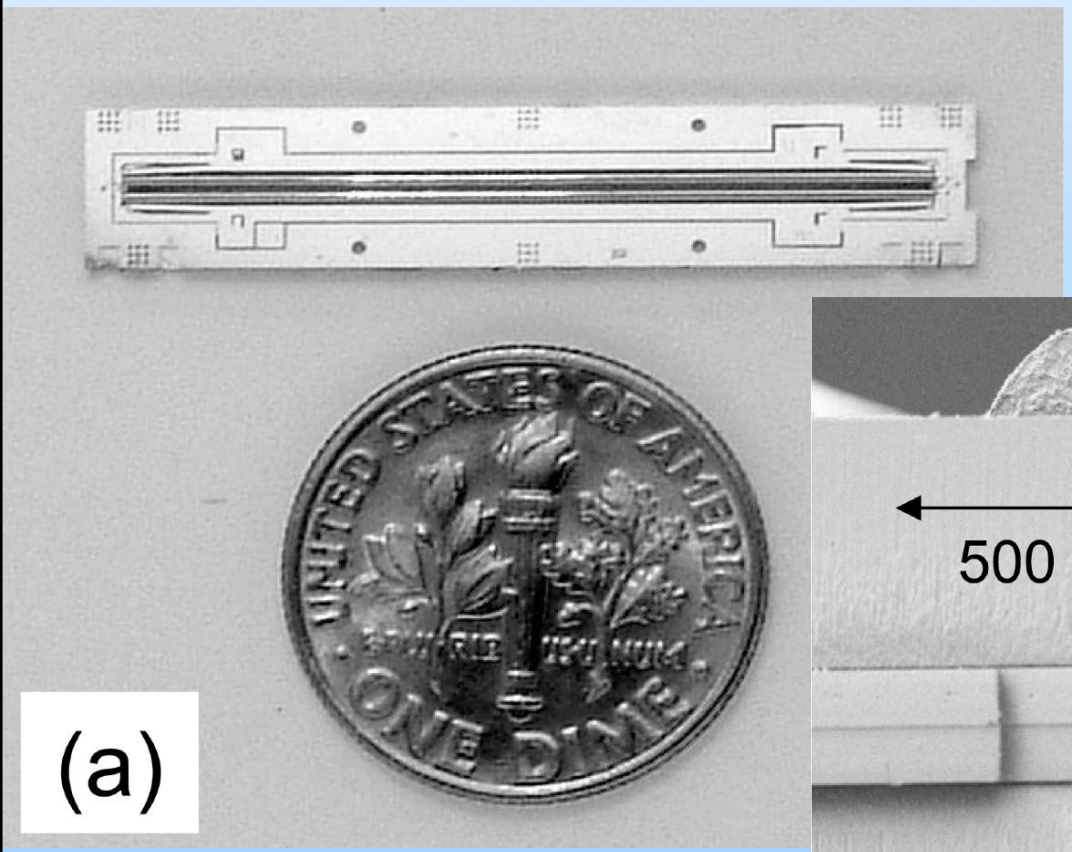
Miniaturized (microfabricated) mass spectrometers?

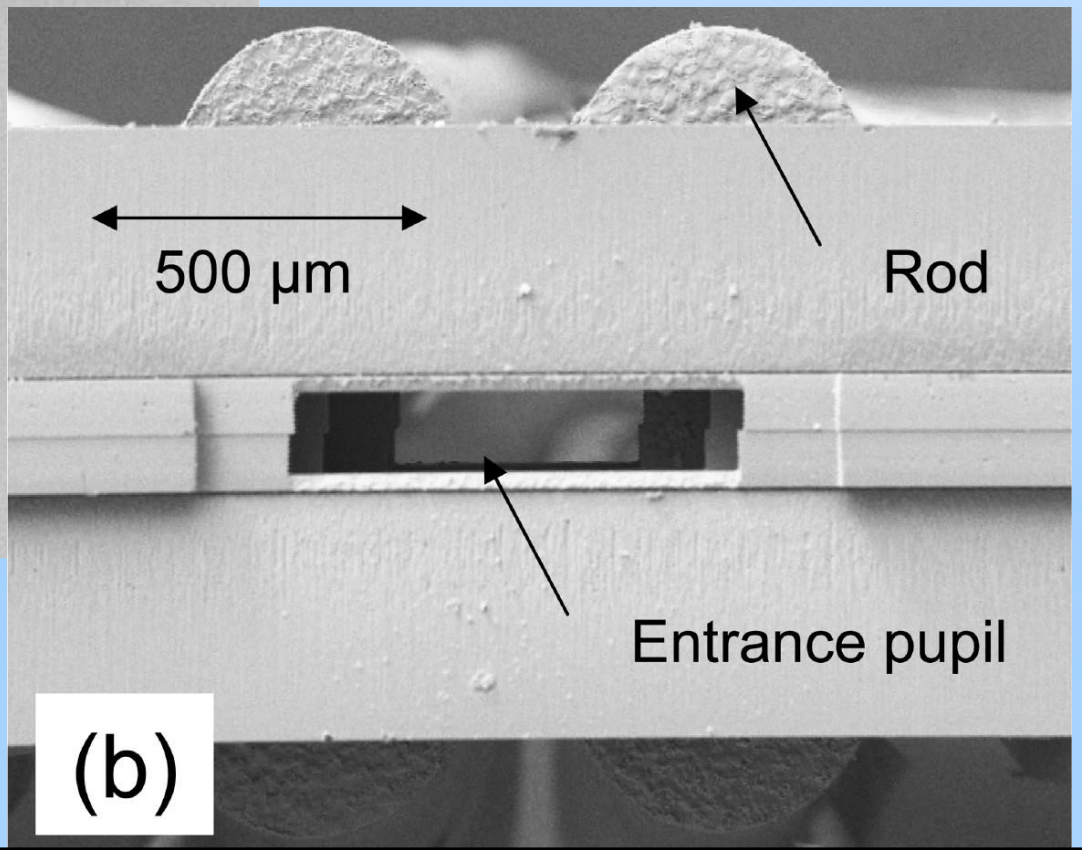


Applications of Miniaturized MS Instruments

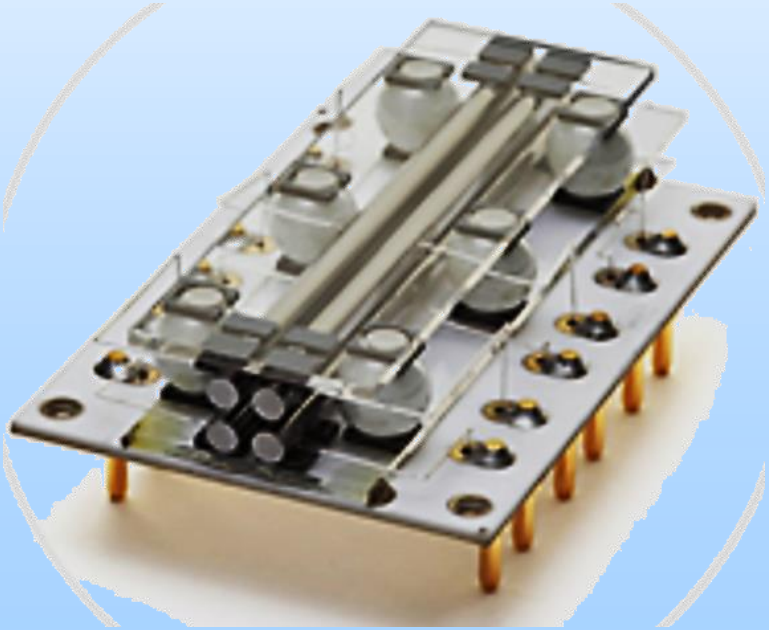
- trace explosive detection and airport security
- space exploration
- environmental monitoring
- point-ofcare medical applications

Miniature Mass Spectrometer Systems based on a Microengineered Quadrupole Filter



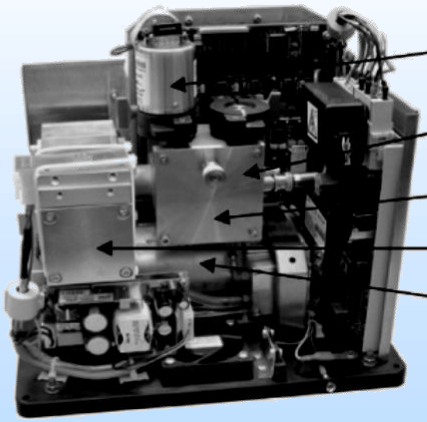


A. Malcolm, S.Wright, R. R. A. Syms, N. Dash, M.-A. Schwab, A. Finlay
Anal. Chem. **2010,** *82,* 1751–1758



Mass Analyzer ionchip® quadrupole mass spectrometer
Mass Range m/z 50-800 with ionchip®150
Mass Accuracy ± m/z 0.3 in full scan
Mass Resolution m/z 0.7±0.1 FWHM
Sensitivity 10pg of reserpine in SIM mode S/N ratio of 10:1 (RMS)

27 cm



Gauge

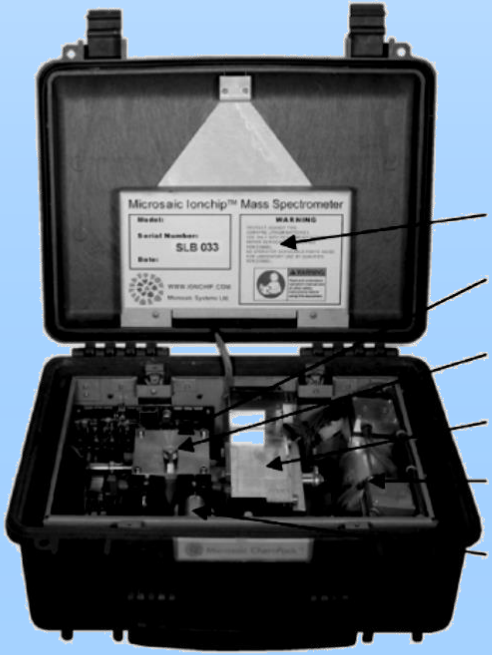
Inlet

Vacuum chamber

Turbo pump

Diaphragm pump

38 cm



Battery

Vacuum chamber

Inlet

Turbo pump

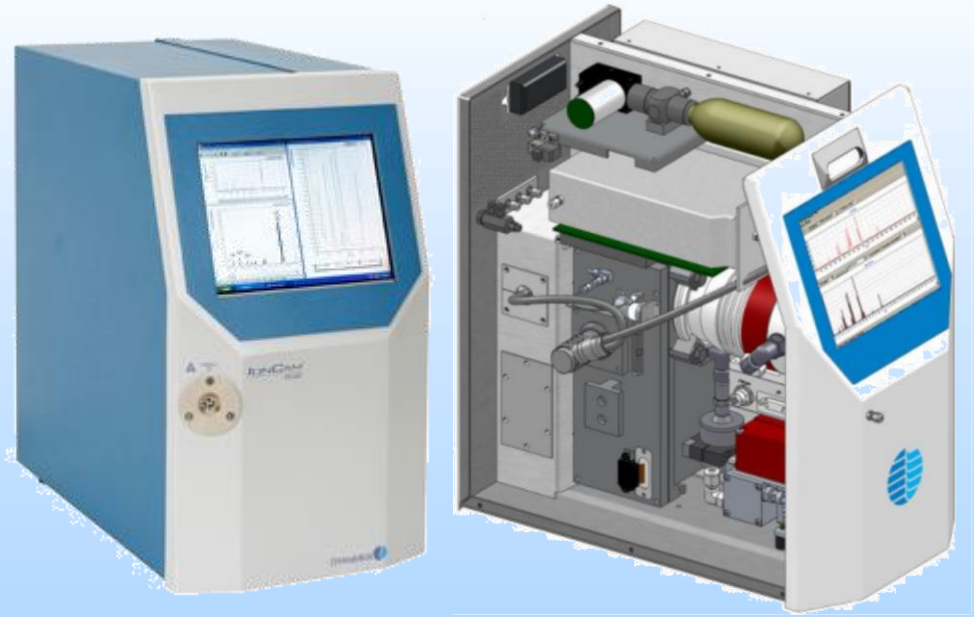
Diaphragm pump

Gauge

Microsaic Systems

4000 MiD Bringing mass spectrometry down to size

www.microsaic.com

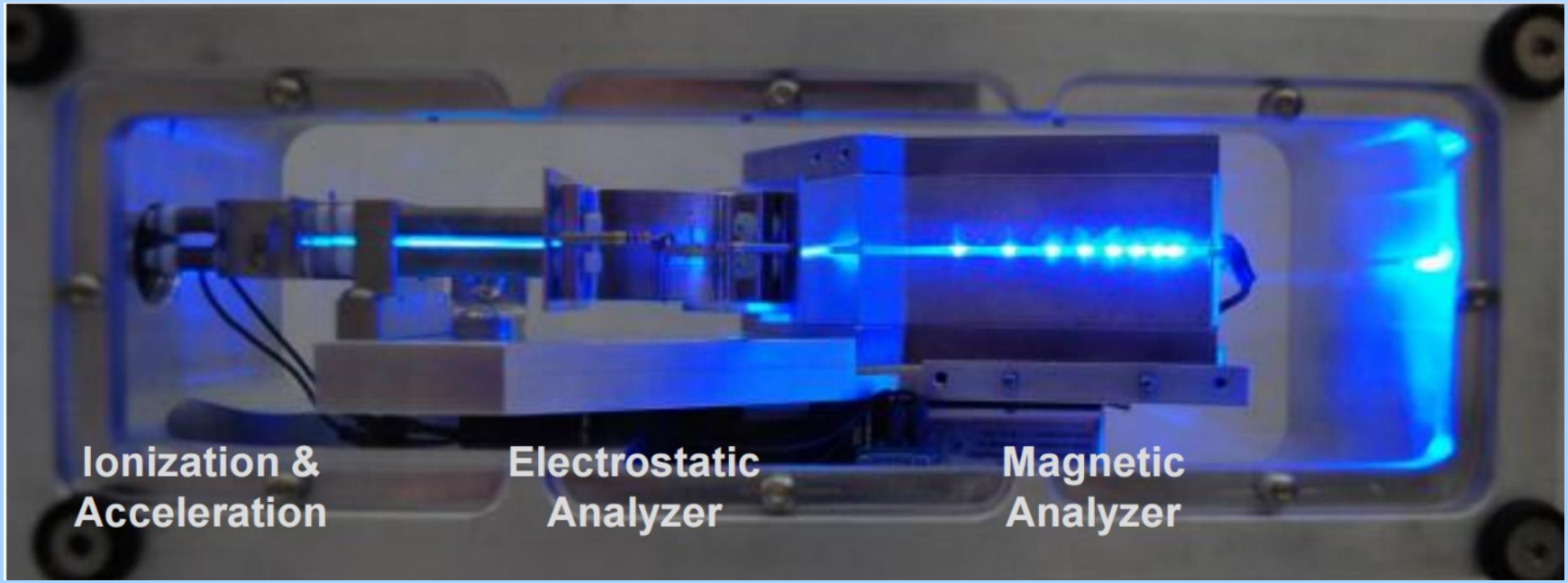


Self-contained instrument

Embedded PC

Vacuum inlet flow 2 mL/min

24V input (battery operation)



OI Analytical, www.oico.com

Advion expression Compact Mass Spectrometer

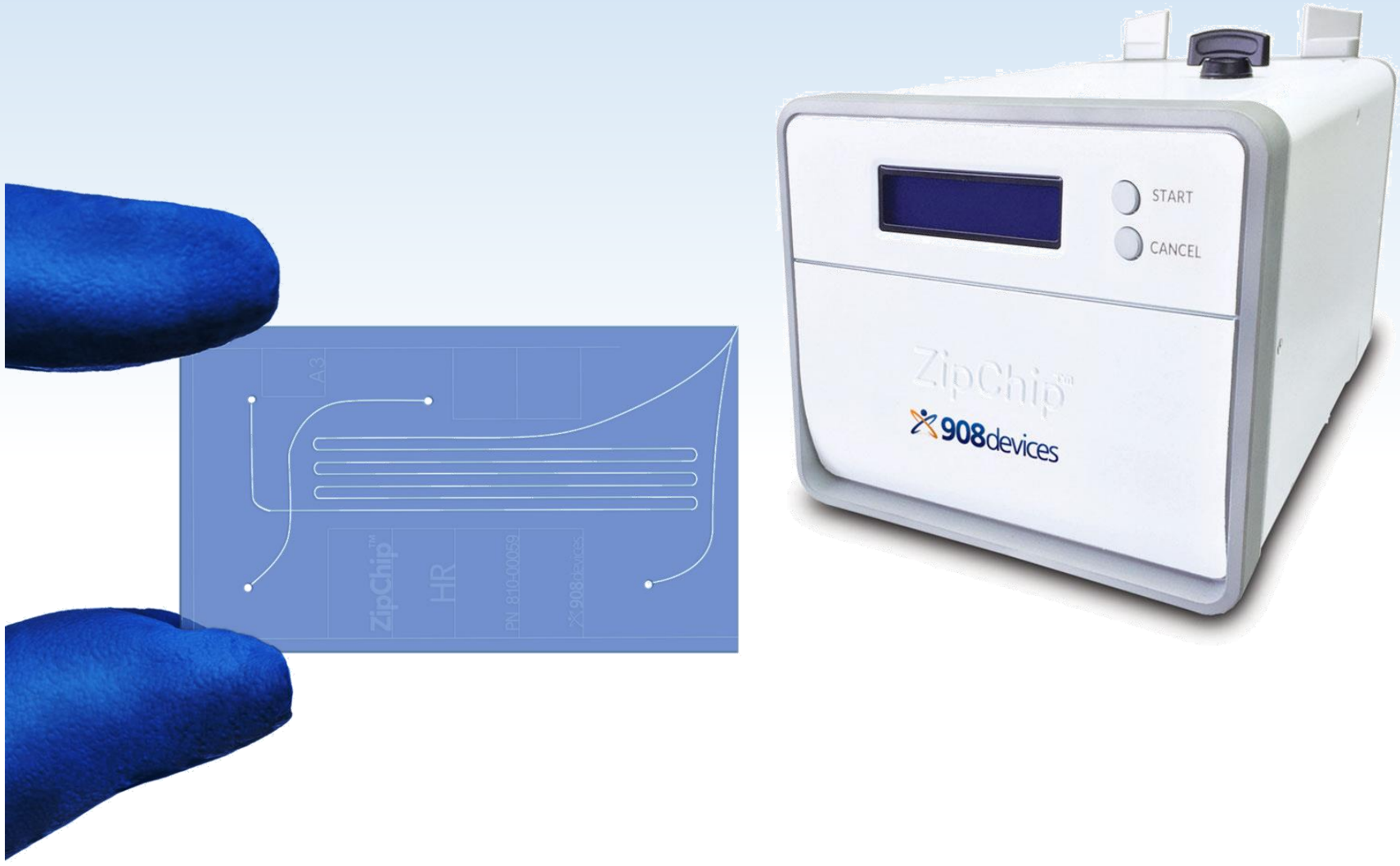
www.advion.com

Microscale Ion Trap

Internal glow discharge ionization
Mass Range 15-450 amu
Mass Resolution 1 amu

http://908devices.com/

Automated CE-MS on a glass chip



Patent? Patent!

What is a patent

Invention disclosure

Does it make sense to patent?

Patent search

Resources

What Is a Patent?

A patent for an invention is the **grant of a property right to the inventor**, issued by the United States Patent and Trademark Office. Generally, the **term of a new patent is 20 years** from the date on which the application for the patent was filed in the United States or, in special cases, from the date an earlier related application was filed, subject to the **payment of maintenance fees.** U.S. patent grants are effective only within the United States, U.S. territories, and U.S. possessions. Under certain circumstances, patent term extensions or adjustments may be available.

What is granted is not the right to make, use, offer for sale, sell or import, but the right to exclude others from making, using, offering for sale, selling or importing the invention. Once a patent is issued, the patentee must enforce the patent without aid of the USPTO.

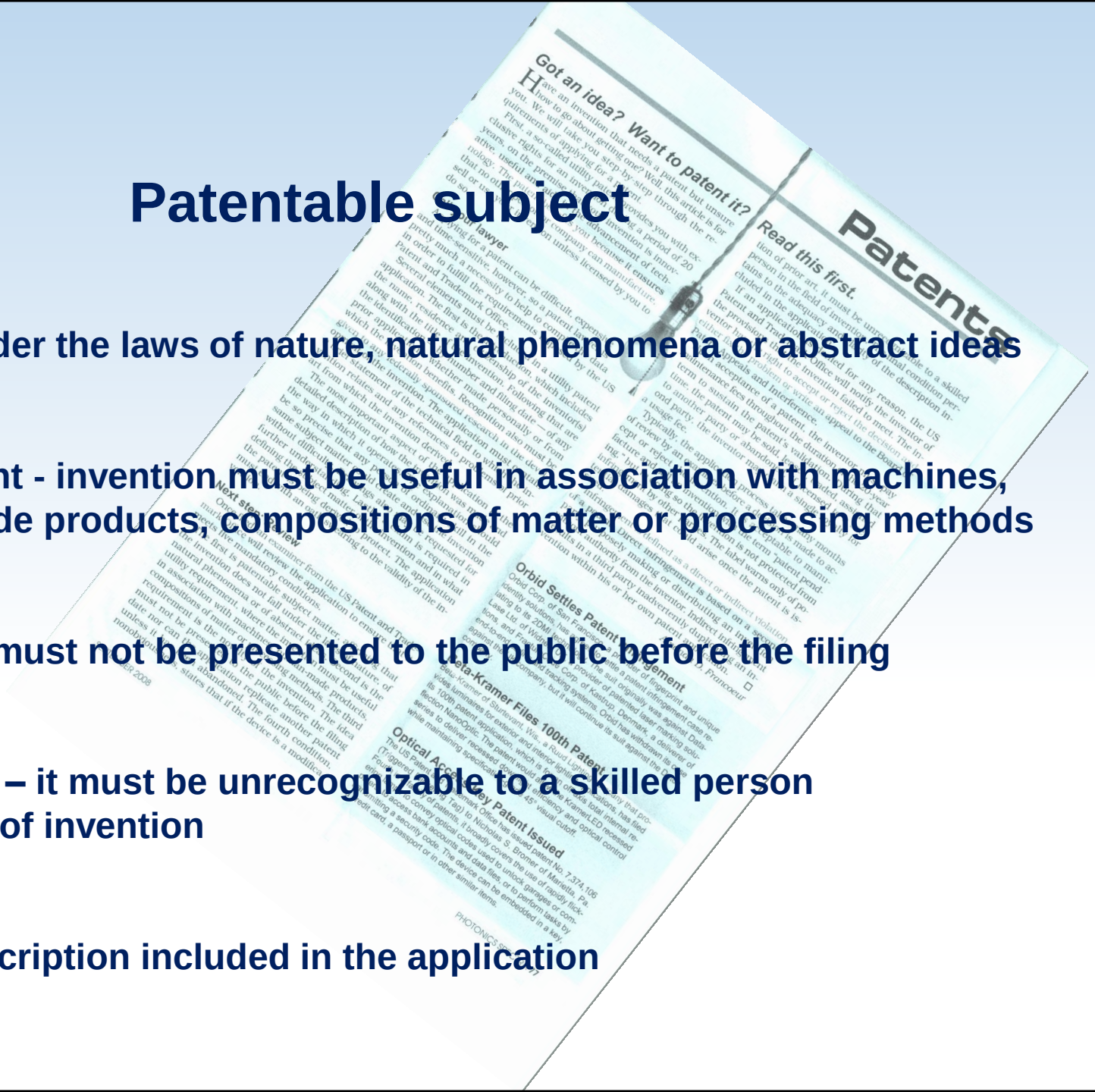
There are **three types of patents**:

1) **Utility patents** may be granted to anyone who invents or discovers any new and **useful process, machine, article of manufacture, or composition of matter**, or any new and useful **improvement thereof**;

2) **Design** patents may be granted to anyone who invents a new, original, and ornamental **design for an article of manufacture**; and

3) **Plant patents** may be granted to anyone who **invents or discovers and asexually reproduces any distinct and new variety of plant.**

Patentable subject



1. Does not fall under the laws of nature, natural phenomena or abstract ideas

2. Utility requirement - invention must be useful in association with machines, human-made products, compositions of matter or processing methods

3. Novelty the idea must not be presented to the public before the filing

4. Nonobviousness – it must be unrecognizable to a skilled person in the field of invention

5. Clarity of the description included in the application

Patent je zákonná ochrana vynálezů zaručující vlastníkovi patentu výhradní právo k průmyslovému využití vynálezu.

V České republice udělování patentů upravuje zákon 527/1990. Podle něj se patenty udělují na vynálezy, které **jsou nové, jsou výsledkem vynálezecké činnosti a jsou průmyslově využitelné**.
Vynález se považuje za nový, jestliže není součástí stavu techniky.

Stavem techniky je všechno, co bylo zveřejněno přede dnem přihlášení patentu, ať již v České republice nebo v zahraničí.

Za vynálezy se naopak nepovažují zejména :

objevy, vědecké teorie a matematické metody,
pouhé vnější úpravy výrobků,
plány, pravidla a způsoby vykonávání duševní činnosti,
programy počítačů,
pouhé uvedení informace

Majitel patentu má výlučné právo vynález využívat (tj. výrobek vyrábět, uvádět do oběhu nebo upotřebit postup), dále poskytnout souhlas k využívání vynálezu jiným osobám (např. licenční smlouvou) a má právo převést patent na jinou osobu.
Proto, aby patent zůstal v platnosti, je nutno platit tzv. udržovací poplatky, a to v každém státu zvlášť. Maximální možná délka patentové ochrany je 20 roků.

http://cs.wikipedia.org/

United States Patent and Trademark Office
www.uspto.gov

European patent office
www.epoline.org

Úřad průmyslového vlastnictví
www.upv.cz

Patents

CRISPR-Cas systems and methods for altering expression of gene products

US 8697359 B1

Publication number	US8697359 B1
Publication type	Grant
Application number	US 14/054,414
Publication date	15 Apr 2014
Filing date	15 Oct 2013
Priority date	12 Dec 2012
Also published as	CA2894688A1, 13 More »
Inventors	Feng Zhang
Original Assignee	The Broad Institute, Inc., Massachusetts Institute Of Technology
Export Citation	BiBTeX, EndNote, RefMan

Patent Citations (9), Non-Patent Citations (9), Referenced by (79), Classifications (44), Legal Events (5)

External Links: USPTO, USPTO Assignment, Espacenet

ABSTRACT

The invention provides for systems, methods, and compositions for altering expression of target gene sequences and related gene products. Provided are vectors and vector systems, some of which encode one or more components of a CRISPR complex, as well as methods for the design and use of such vectors. Also provided are methods of directing CRISPR complex formation in eukaryotic cells and methods for utilizing the CRISPR-Cas system.

IMAGES (46)

DESCRIPTION

RELATED APPLICATIONS AND INCORPORATION BY REFERENCE

This application claims priority to U.S. provisional patent application 61/842,322, entitled CRISPR-CAS SYSTEMS AND METHODS FOR ALTERING

CLAIMS (20)

What is claimed is:

1. A method of altering expression of at least one gene product comprising introducing into a eukaryotic cell containing and expressing a DNA molecule

US00D366297S

United States Patent [19]

Ford

[11] Patent Number: Des. 366,297

[45] Date of Patent: **Jan. 16, 1996

[54] **FINGER PUPPET**

[75] Inventor: **Hobart Ford**, 62 Ballard Ranch Rd., Weaverville, N.C. 28787

[73] Assignees: **Hobart Ford**, Weaverville, N.C.; **Regina Marscheider**, Virginia Beach, Va.

[**] Term: **14 Years**

[21] Appl. No.: **20,759**

[22] Filed: **Apr. 1, 1994**

[52] **U.S. Cl.** **D21/153**; D21/189

[58] **Field of Search** D21/148, 149, D21/152, 153, 189–190; 446/71, 72, 83, 97, 268, 392, 327

[56] **References Cited**

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4,304,065	12/1981	Balera	446/327
4,409,754	10/1983	Moreau	446/392

FOREIGN PATENT DOCUMENTS

431066	8/1911	France	446/392
753289	8/1933	France	466/392

Primary Examiner—Sandra L. Morris
Attorney, Agent, or Firm—Lowe, Price, LeBlanc & Becker

[57] **CLAIM**

The ornamental design for a finger puppet, as shown and described.

DESCRIPTION

FIG. **1** is a reduced perspective view of a finger puppet, showing my new design, the broken line showing of a hand is for illustrative purposes only, and forms no part of the claimed design;

FIG. **2** is a front elevational view thereof;

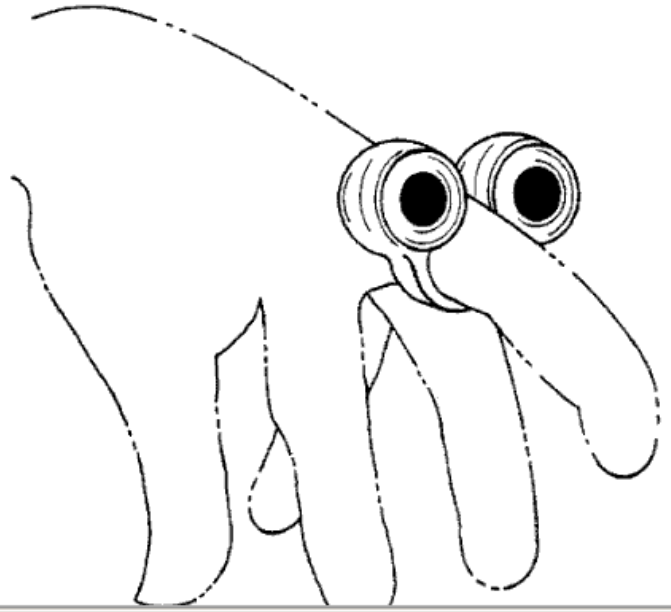
FIG. **3** is a rear elevational view thereof;

FIG. **4** is a bottom plan view thereof;

FIG. **5** is a top plan view thereof; and,

FIG. **6** is a side elevational view thereof, both sides being of the same appearance.

1 Claim, 1 Drawing Sheet



CTT
Centrum pro transfer technologií

Firmy a firemní zákazníci

Vědci a studenti univerzity

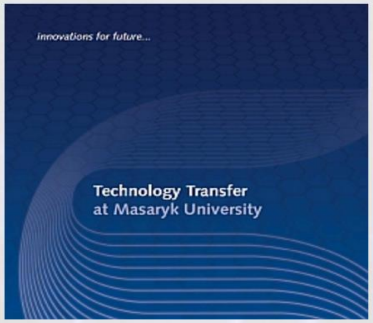
Centrum pro transfer technologií Masarykovy univerzity (CTT) bylo založeno v roce 2005 s jednoznačným posláním: podporovat uplatnění výsledků vědy a výzkumu v praxi, budovat mosty mezi akademickou a soukromou sférou, nastavovat podmínky pro transfer technologií a znalostí, chránit a spravovat duševní vlastnictví MU a poskytovat vědcům i firmám profesionální podporu a servis ve všech souvisejících oblastech.

Tým CTT je tvořen business development manažery, projektovými manažery, právníky a ekonomicko-administrativním zázemím. Portfoliem svých služeb tito specialisté oslovují jak vědce MU, tak komerční firmy. Jaké jsou základní úkoly pracoviště?

- primární kontaktní místo Masarykovy univerzity pro firmy
- zprostředkování spolupráce akademické a podnikatelské sféry
- podpora uplatnění výsledků výzkumu v praxi
- ochrana a správa duševního vlastnictví
- propagace výzkumných aktivit Masarykovy univerzity
- vzdělávání a poradenství v oblasti transferu technologií a duševního vlastnictví

Více informací o transferu technologií na Masarykově univerzitě se dozvíte z brožury CTT. Příslušnou jazykovou verzi otevřete kliknutím na obrázek.

Česká verze brožury



Anglická verze brožury

www.ctt.muni.cz

Novinky a akce

9.11.2016
Vychází druhý letošní INTERFACE
Právě vychází druhé letošní číslo zpravodaje INTERFACE, který vydává Centrum pro...

2.11.2016
TT Day 2016: Vstupte do světa inovací!
Centrum pro transfer technologií si Vás dovoluje pozvat na 4. den otevřených dveří ...

31.10.2016
Pozor na podvodné prodlužování ochranných známek!
Na CTT MU opět přišly dokumenty, které se tváří jako výzva k prodloužení ochranné...

13.10.2016
MU spolupořádá konferenci o mezinárodních dotačních programech
Masarykova univerzita zve jako spolupořadatel na konferenci s názvem "Neříkejte NE...

Kontakt

Masarykova univerzita
Centrum pro transfer technologií

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CECE 2018 15th International Interdisciplinary Meeting on Bioanalysis

Brno, October 15 - 17, 2018

Brno, No. 27 on the list of 52 places to visit in 2016

The New York Times

www.ce-ce.org