Laboratory Director's
Distinguished Lecture Series

Pacific Northwest
NATIONAL LABORATORY

Dr. R. Graham Cooks

Distinguished Professor of Chemistry
Purdue University

Extending the Boundaries of Mass Spectrometry: Analysis, Synthesis, and Materials Preparation

March 25, 2014

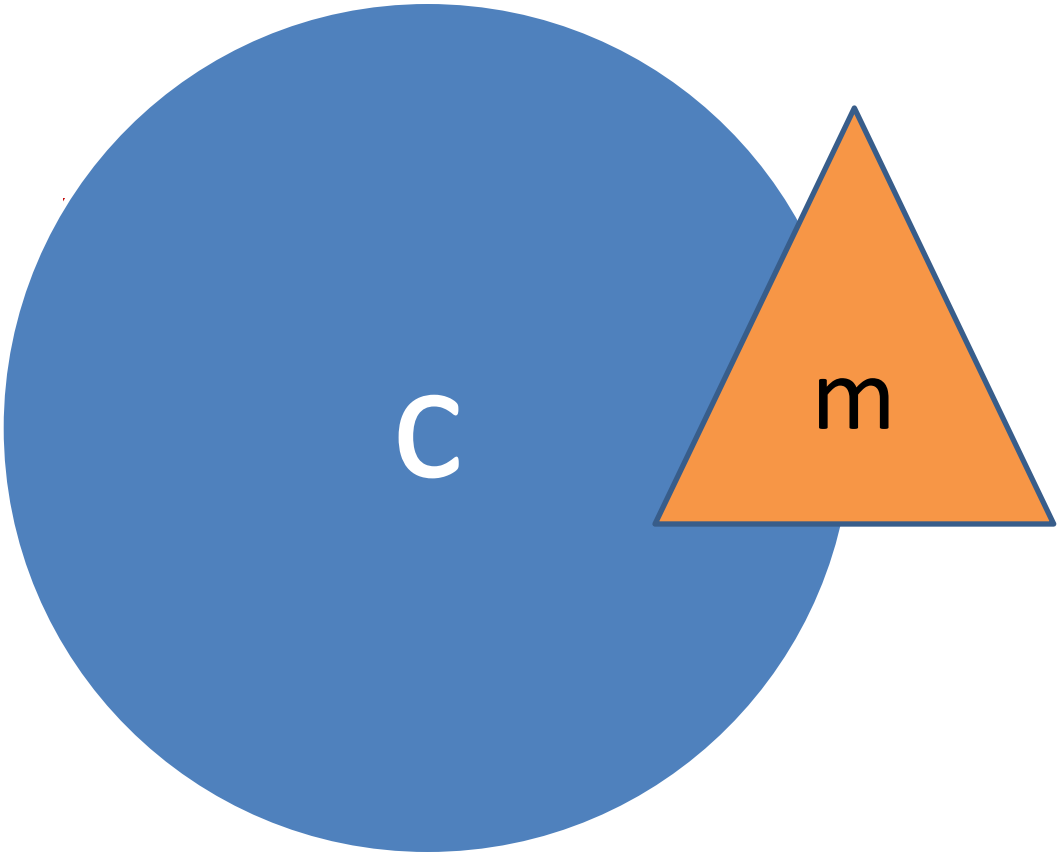
Pacific Northwest National Laboratory
Richland, WA
http://regionaloutreach.pnnl.gov/lectures/

.

~ 13.6 bYr

A singularity occurs

~ 13.6 bYr + 2 psec



Mass spectrometry begins

~ 13.6 bYr

-

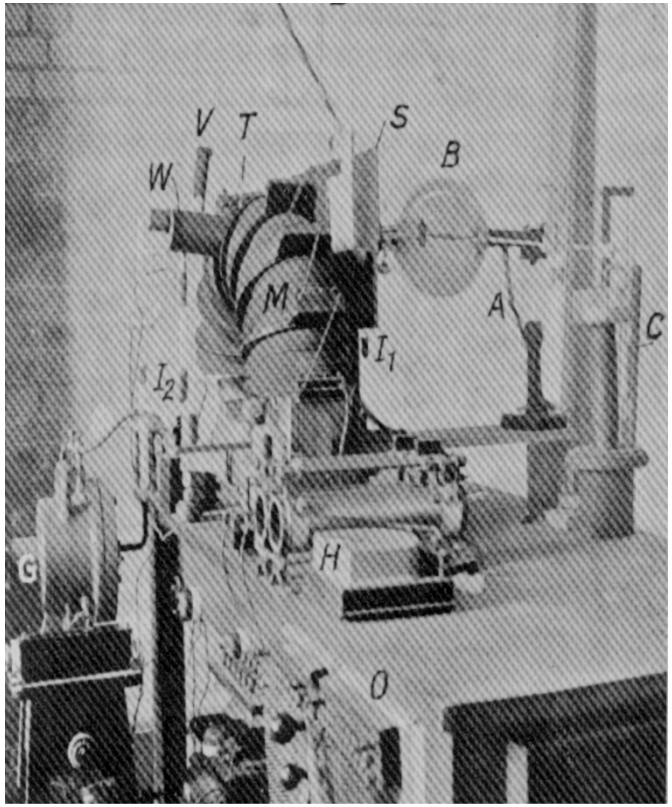
~ 4.6 bYr

Solar system forms; local production of ions

Ionian Sea

~ 13.6 bYr

-



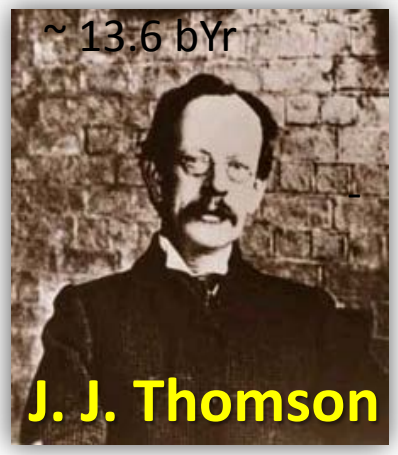
~ 4.6 bYr

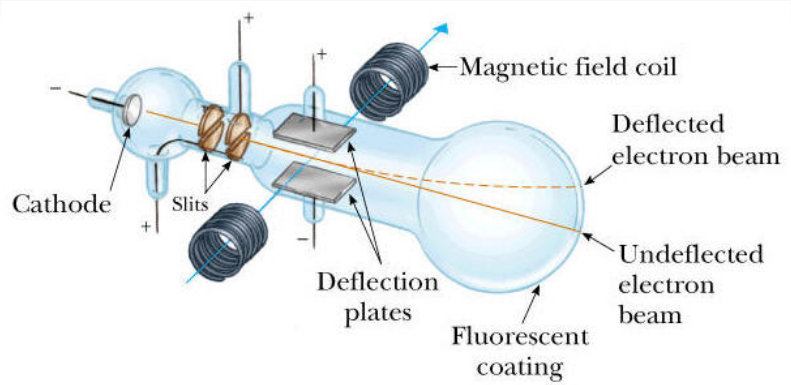
Crookes, Rontgen, Wien, Thomson

1870 - present

First artificial production of ions

Origins of Mass Spec: 19th C Physics





http://www.physics.byu.edu/faculty/christensen/Physics%20220/FTI/29%20Magnetic%20Fields/29.24%20Electron%20e%20to%20m%20ratio.htm

http://www.crtsite.com/page3.html

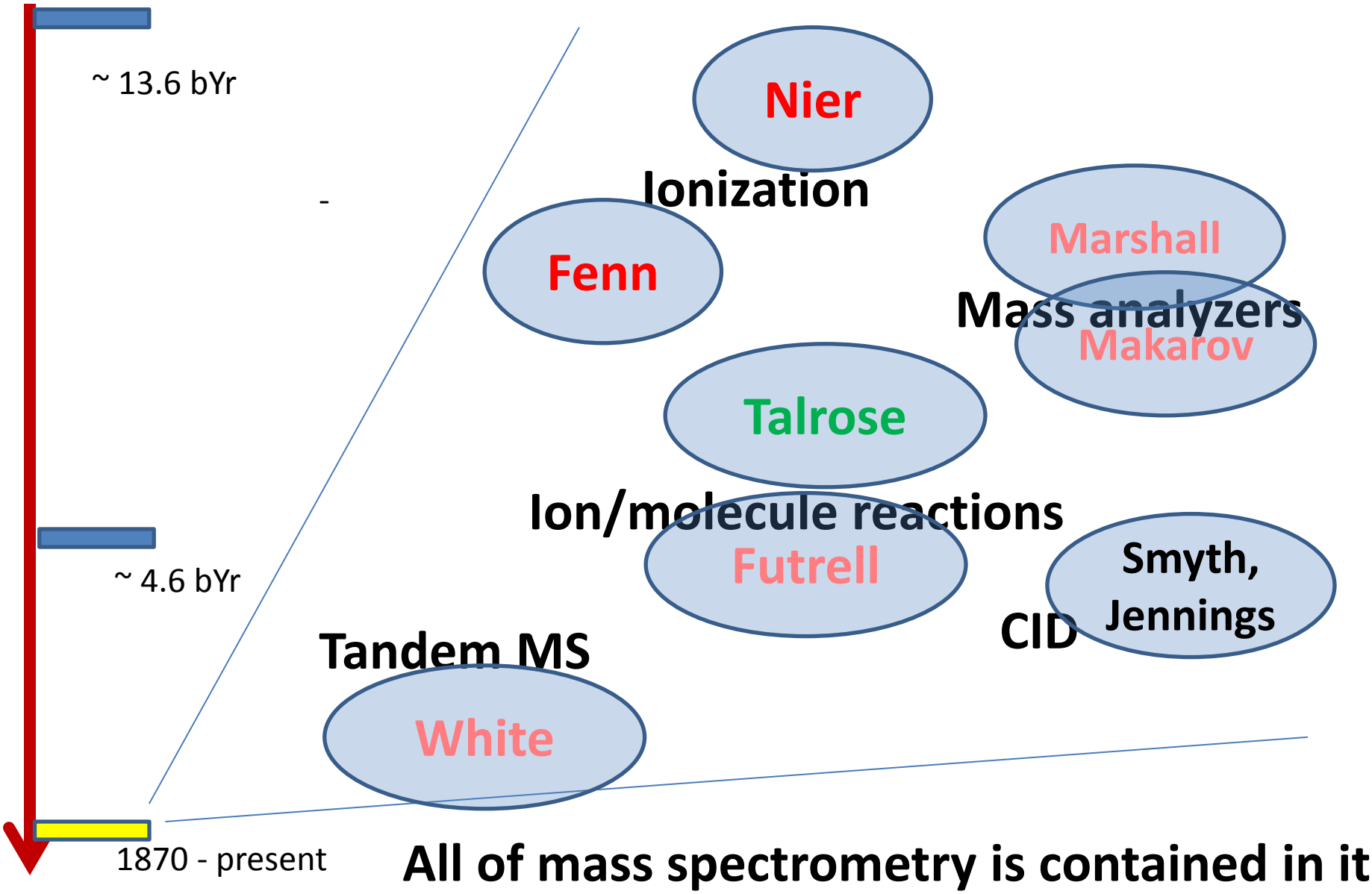
MAGNETIC FIELD → e^- → **ELECTRONICS** → **"Technology"** → **MODERN WORLD**

$\frac{1}{1840}$ of H atom

~ 4.6 bYr

ELECTRIC FIELD → **ion** → **MASS SPECTROMETRY** → **Isotopes, Nuclear Power, Thermochemistry, Chemical Analysis, Biological Measurements** → **FUTURE?**

1870 - present

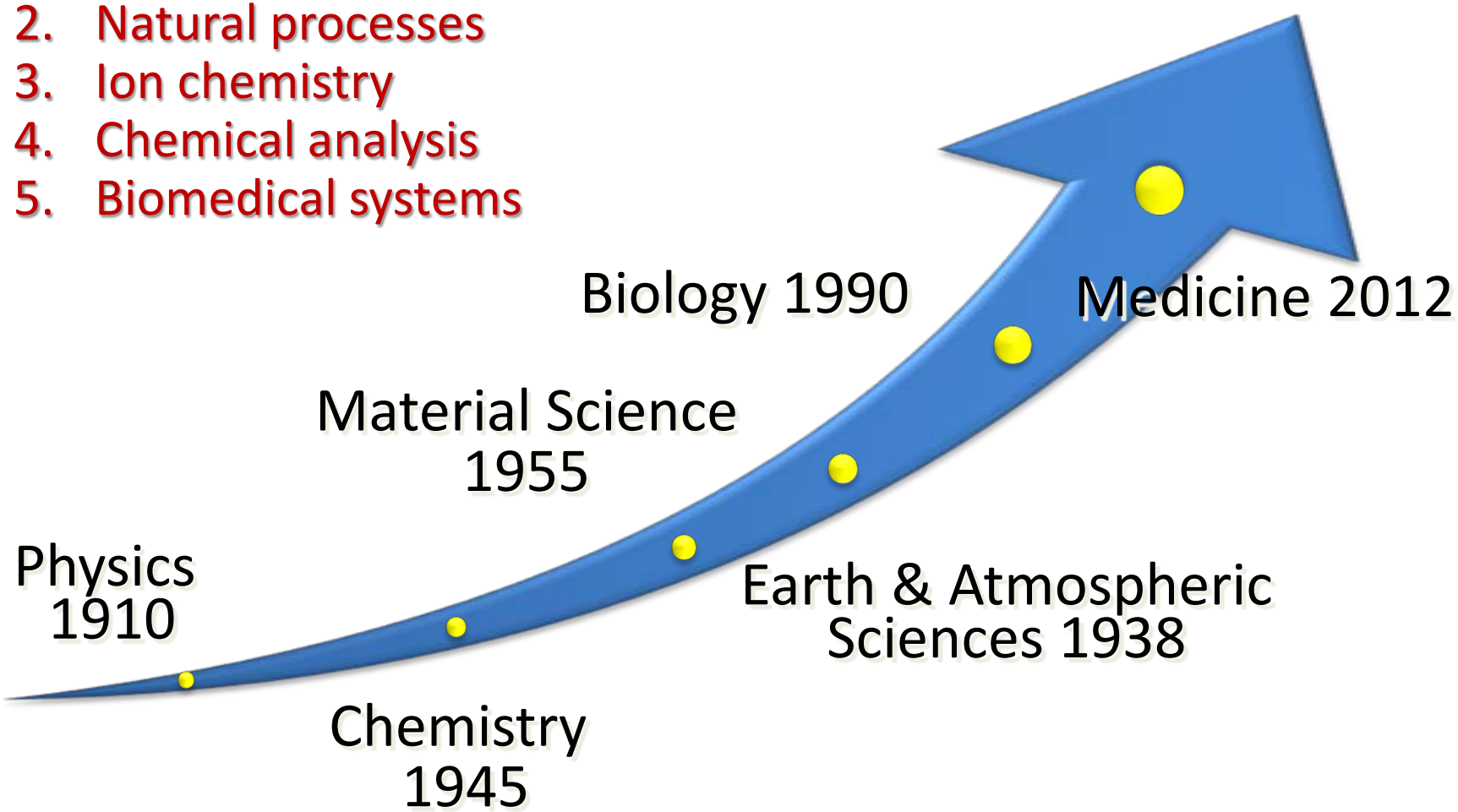


All of mass spectrometry is contained in it

Mass Spectrometry Moves across the Disciplines

Questions:

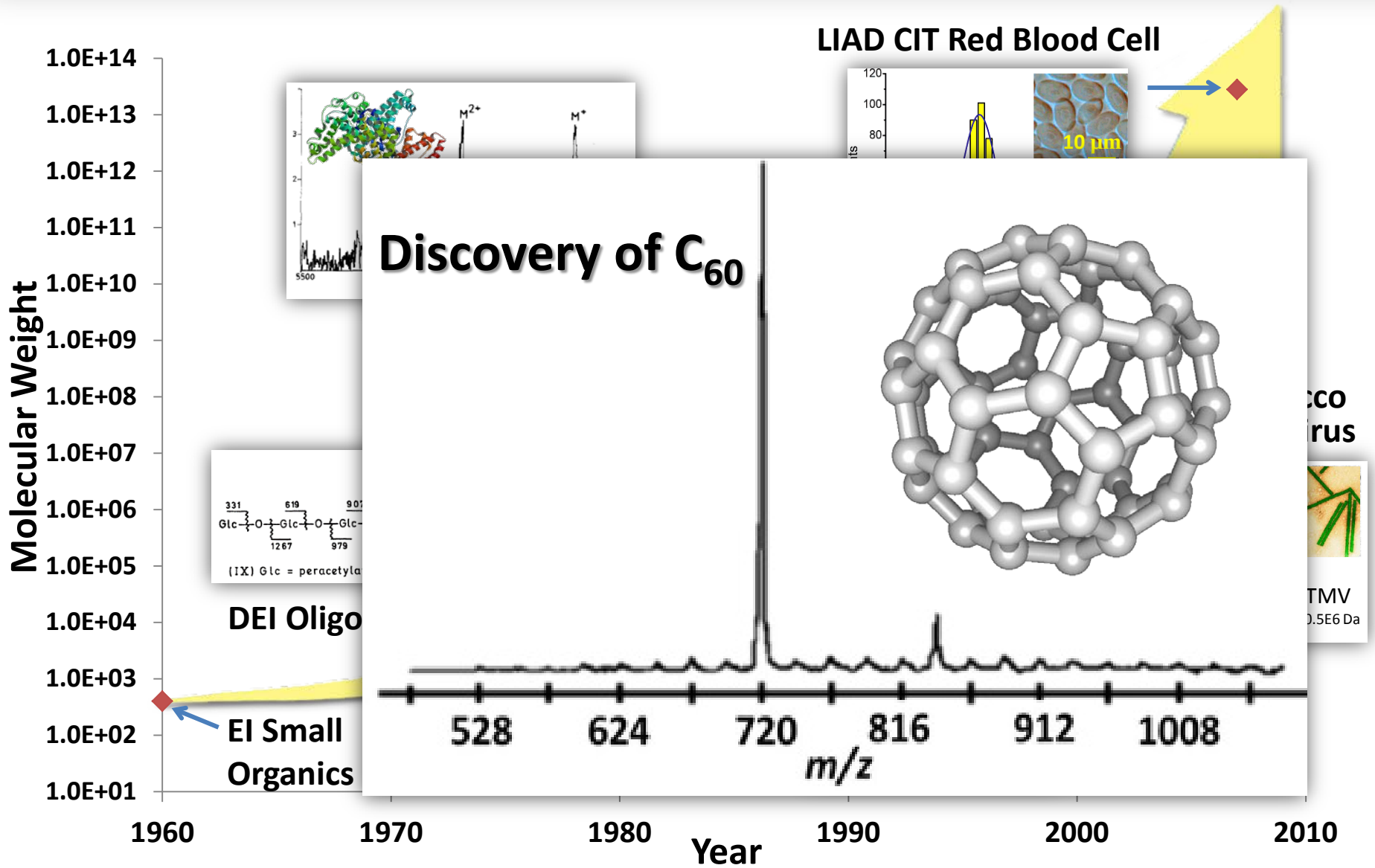
1. Nature of matter
2. Natural processes
3. Ion chemistry
4. Chemical analysis
5. Biomedical systems



Major Impacts of Mass Spectrometry (Top 10)

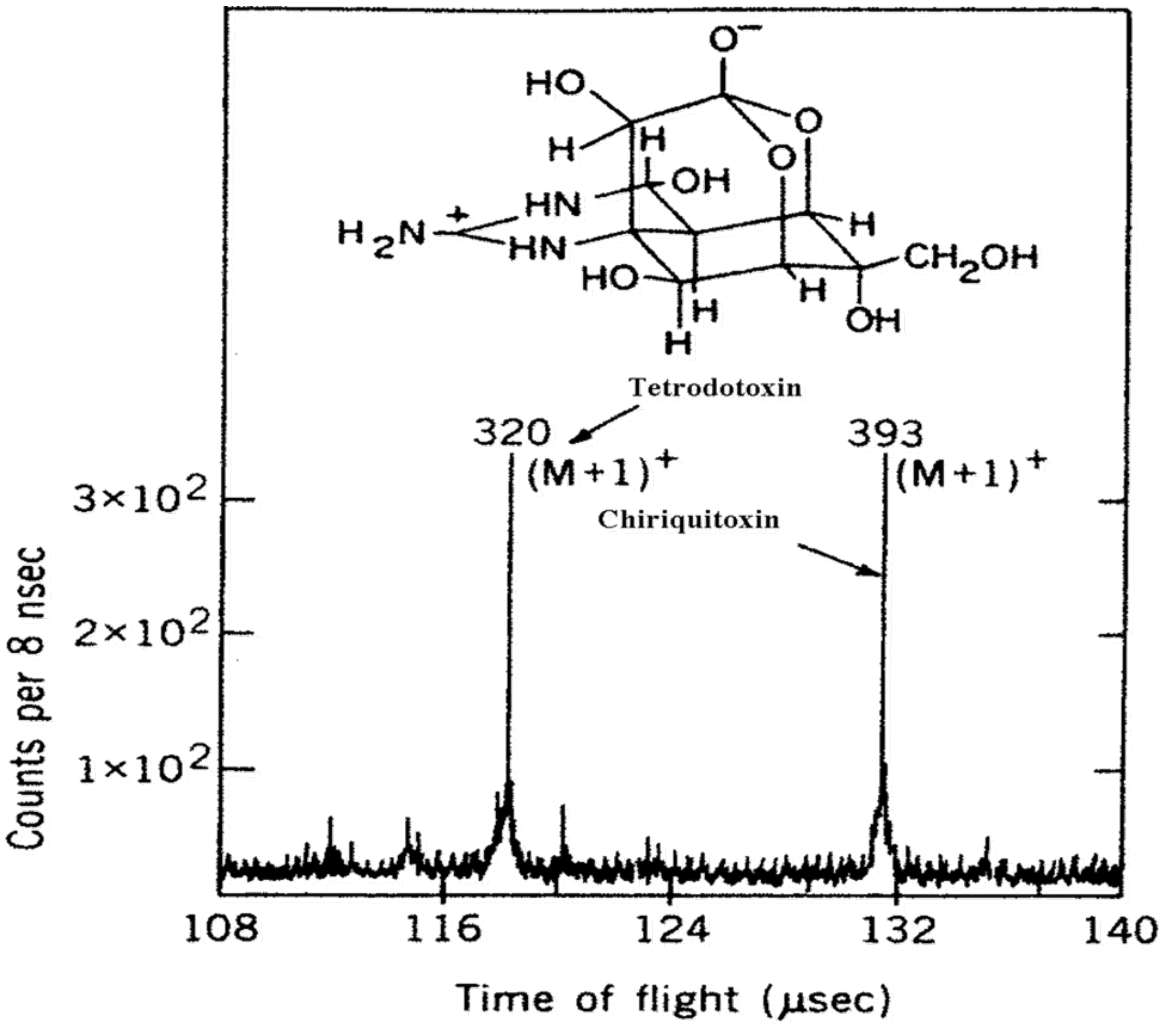
Atomic structure
Thermochemistry
Isotopes and tracer studies
Environmental sciences
Proteomics & lipidomics & metabolomics
Drug discovery
Physical organic chemistry
Toxicology
Surface analysis & modification
Natural products chemistry & Cluster science

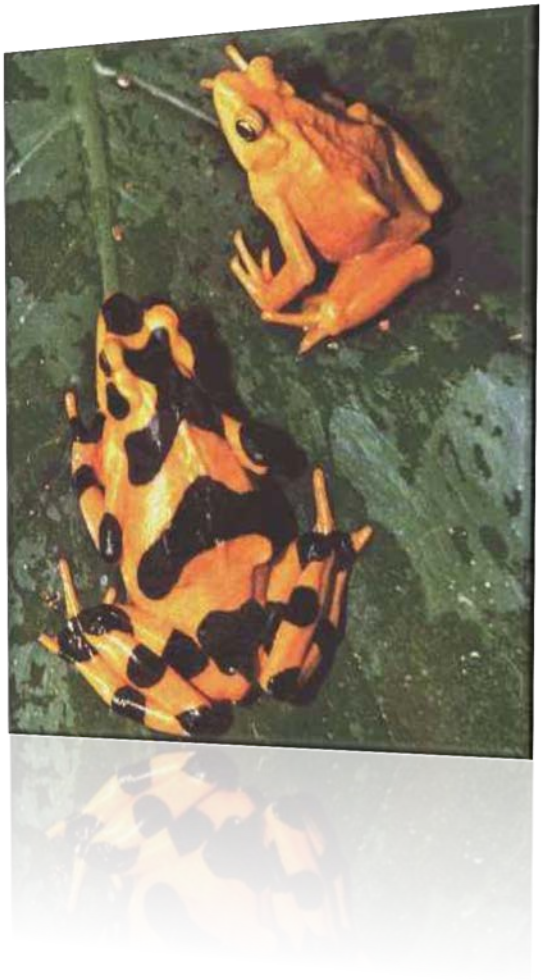
Driving Forces in MS: Higher Mass



Transition to Biology

PDMS Amazon frog toxin



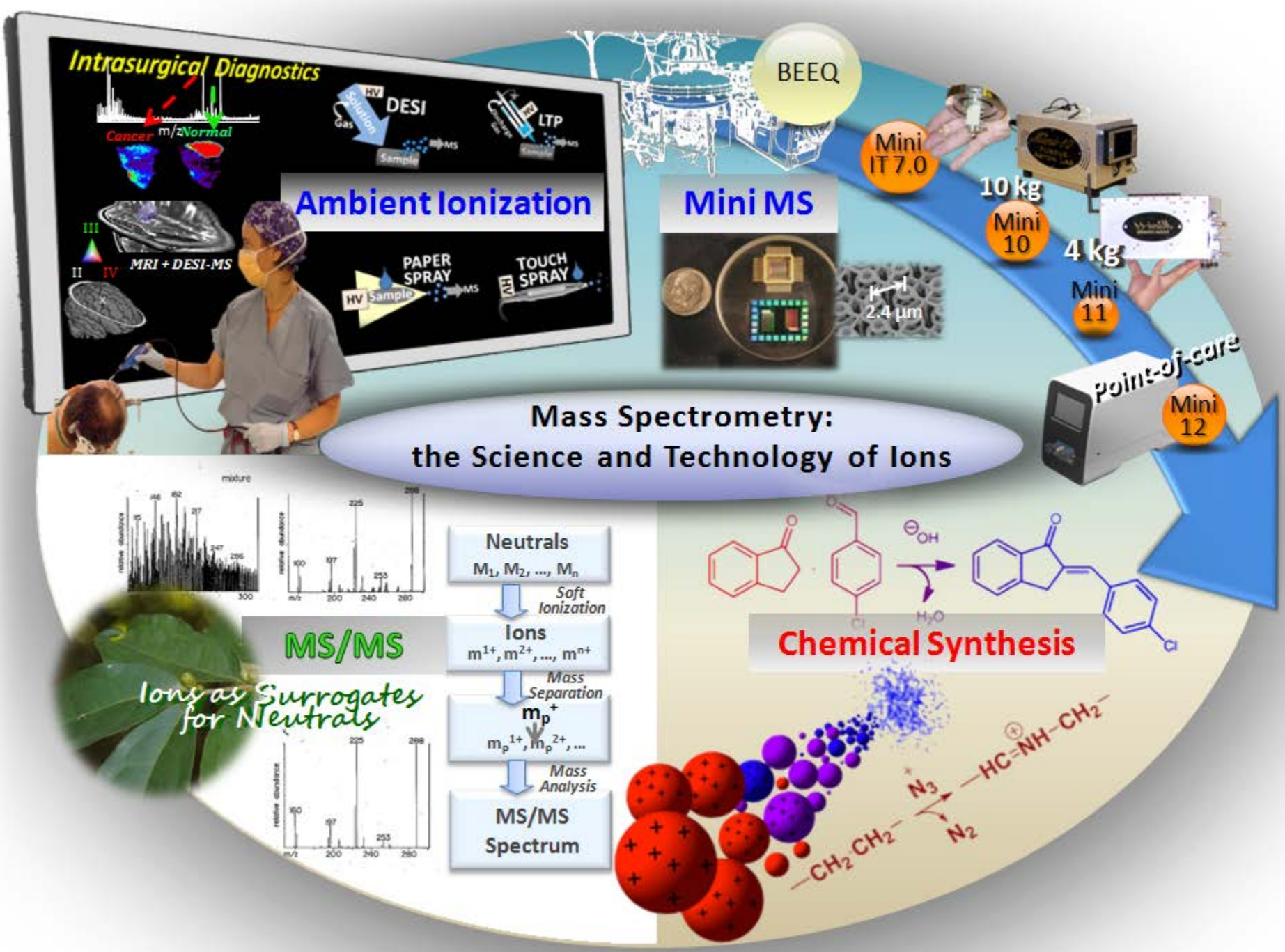


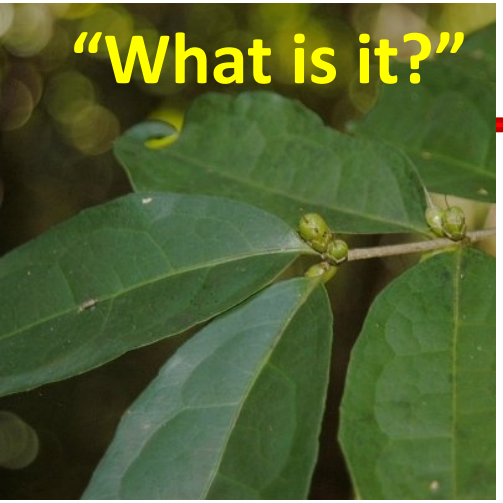
Macfarlane 1976

Singular Discoveries in MS

Mass electron	Thomson
^{22}Ar	Aston
Double focusing	Nier
Appearance energy	Stevenson
CH_5^+ (1st ion/molecule reaction)	Talrose
Metastable ions	Condon
QET (unimolec. rxn. kinetics)	Rosenstock
Ion trap	Paul
$(H_2O)_nH^+$ (Ionic equilibria)	Kebarle
Solvation & acidity/basicity	Brauman

Top 10 through 1975

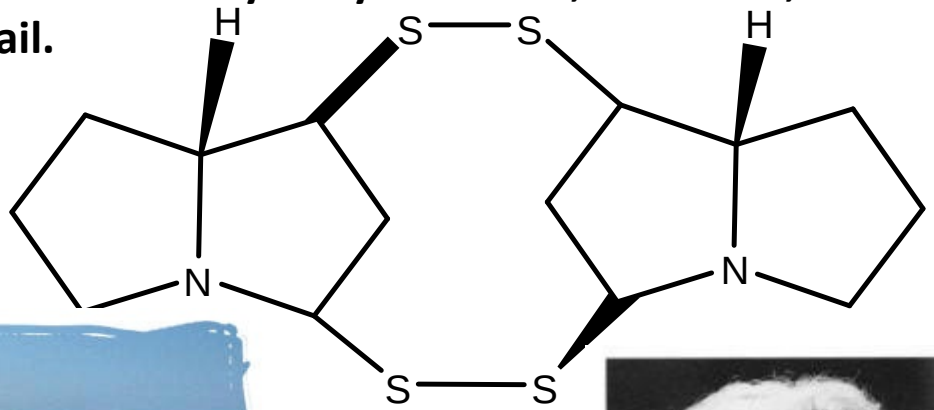

Intrasurgical Diagnostics
Cancer
m/z
Normal
MRI + DESI-MS
DESI
LTP
Ambient Ionization
PAPER SPRAY
TOUCH SPRAY
BEEQ
Mini MS
2.4 µm
Mini IT 7.0
10 kg
Mini 10
4 kg
Mini 11
Point-of-care
Mini 12
Mass Spectrometry:
the Science and Technology of Ions
Neutrals
$M_1, M_2, ..., M_n$
Soft Ionization
Ions
$m^{1+}, m^{2+}, ..., m^{n+}$
Mass Separation
m_p^+
$m_p^{1+}, m_p^{2+}, ...$
Mass Analysis
MS/MS Spectrum
MS/MS
Ions as Surrogates for Neutrals
Chemical Synthesis



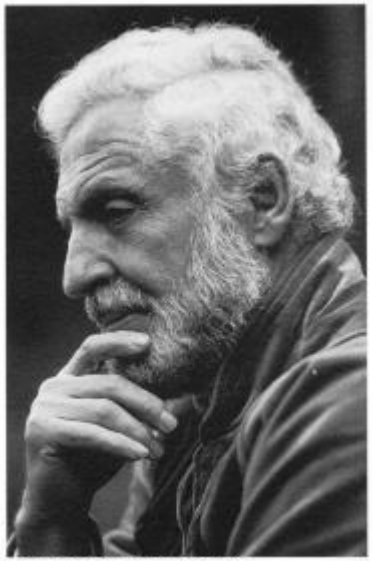
Natural Products -- Long ago & Far Away

Using a chain saw, biologist + land rover gave 8kg bark, which was pulverized, extracted with chloroform, Extract was chromatographed on 25cm diam column on cellulose then on Al_2O_3 giving 1,5 g impure alkaloid mixture

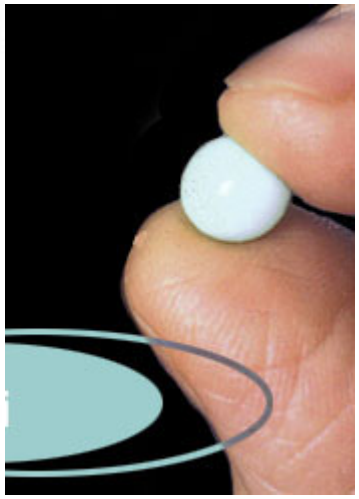
Structural analysis by oxidation, reduction, Hoffmann elimination, to no avail.



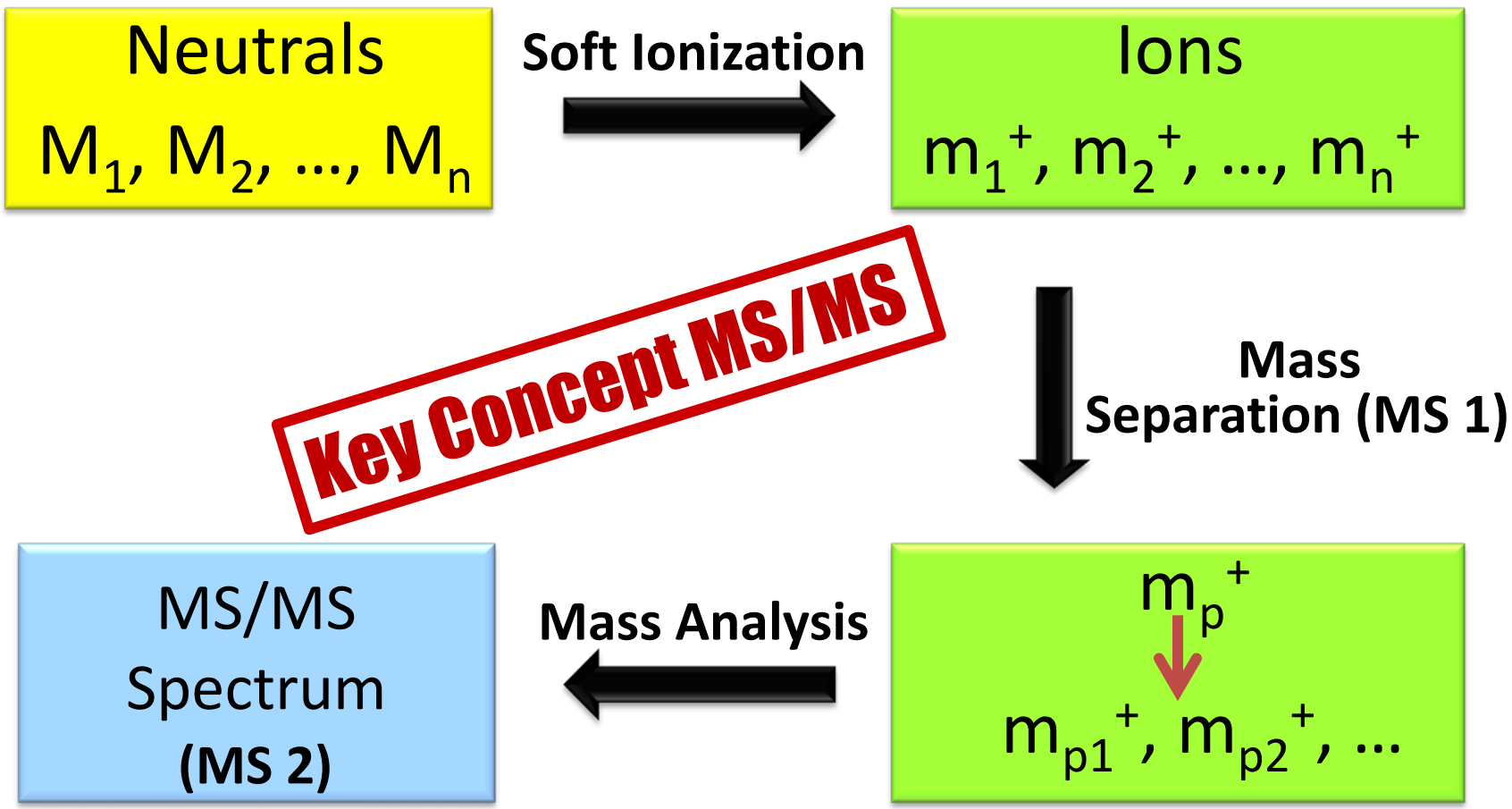
Cassipourea (mangrove)



Photographer: Margo Davis



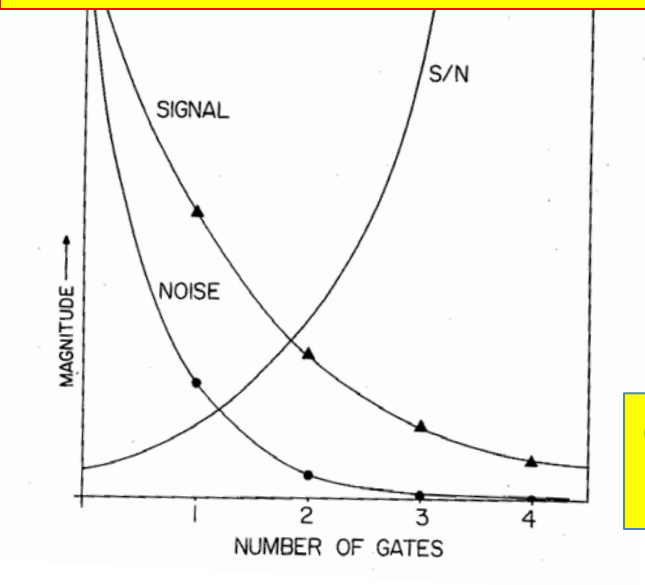
Ions as Surrogates for Neutrals (1976)

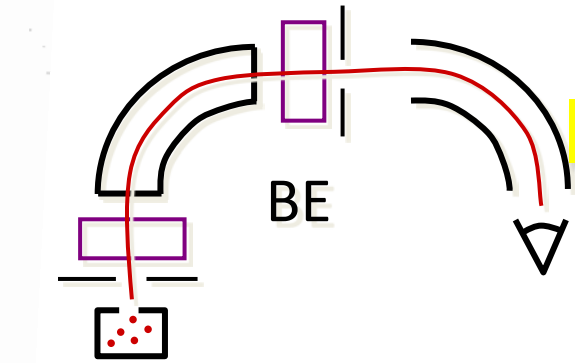


Kondrat and R.G. Cooks, *Anal. Chem.*, **1978**, *50*, A81

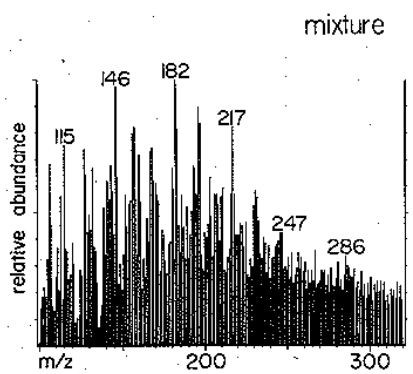
Complex mixtures– Soft Ionization + MS/MS

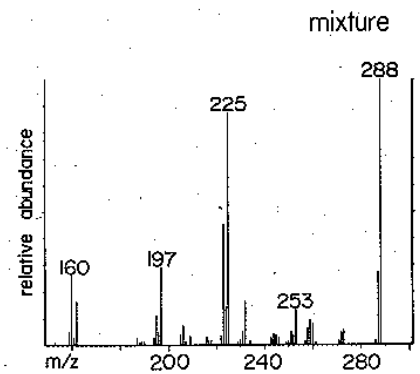
MS/MS (MIKES) plus gentle ionization
molecular ions are surrogates for neutrals ---
So complex mixture analysis





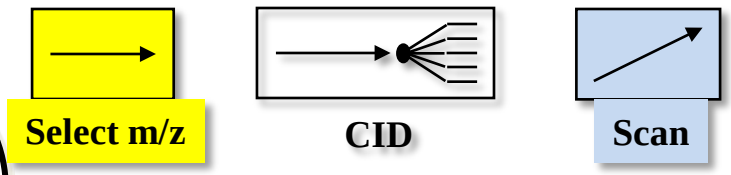
CI soft Ion source



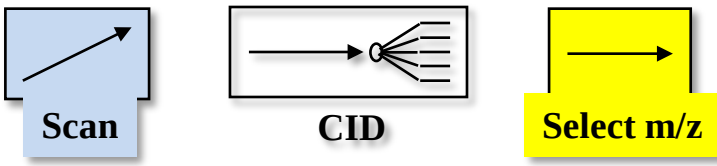


MS/MS

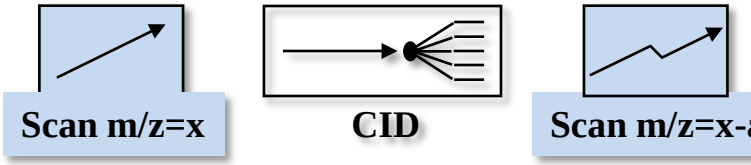
Product Ion Scan



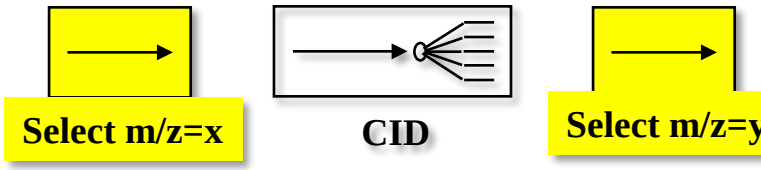
Precursor Ion Scan



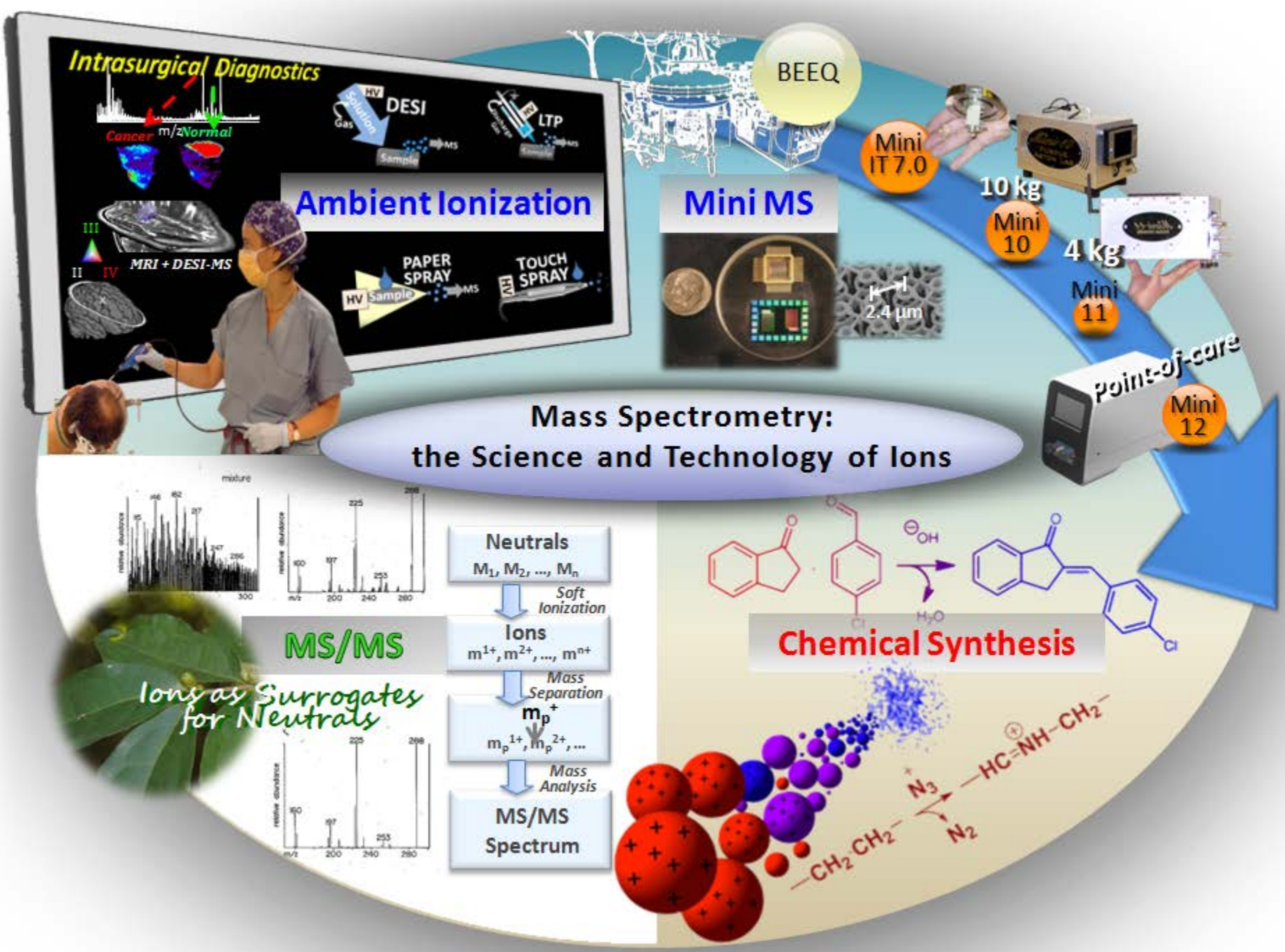
Neutral Loss Scan



Multiple Reaction Monitoring

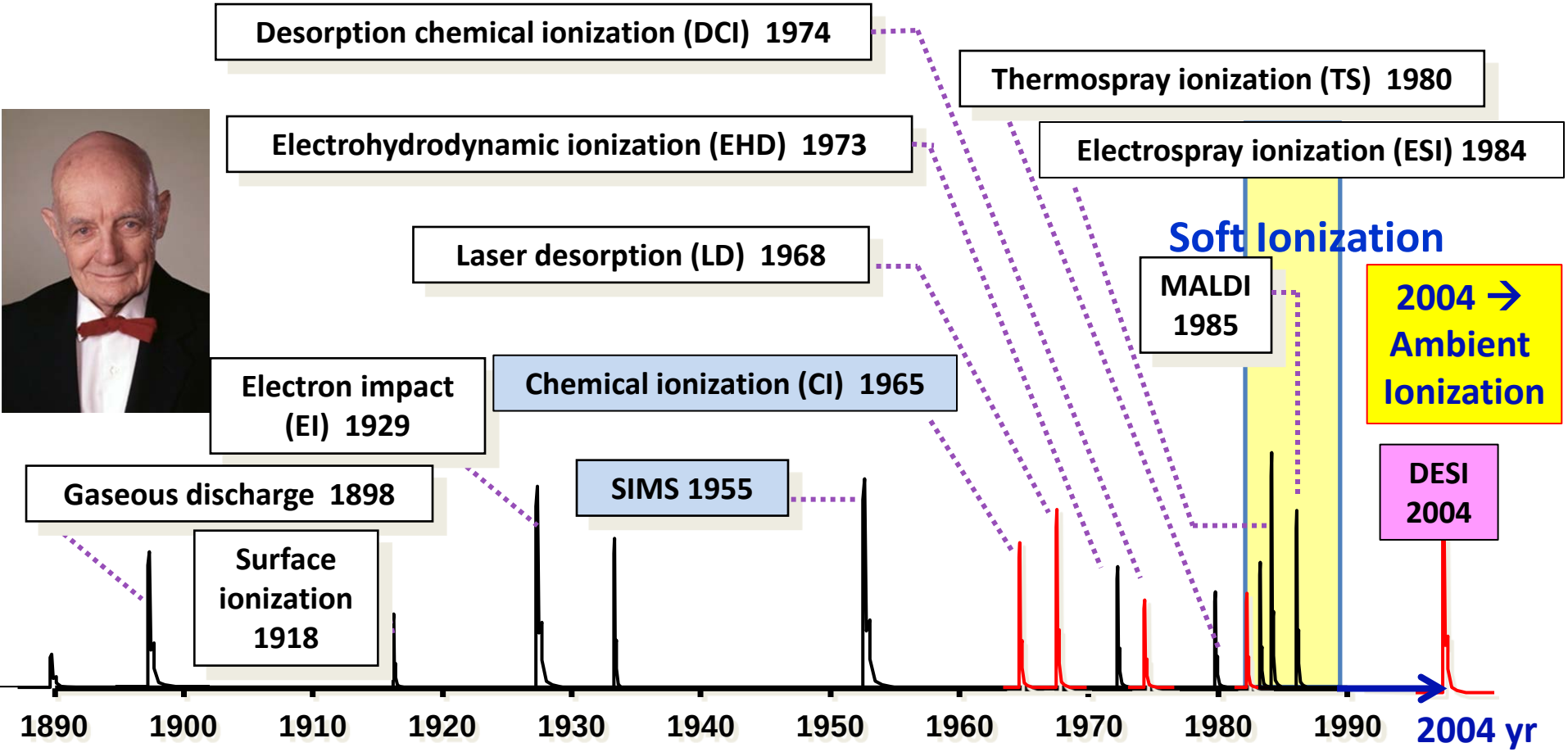


Cooks and Kondrat, Anal. Chem. 1978;


Intrasurgical Diagnostics
Cancer
m/z
Normal
MRI + DESI-MS
DESI
LTP
Ambient Ionization
PAPER SPRAY
TOUCH SPRAY
BEEQ
Mini MS
2.4 µm
Mini IT 7.0
10 kg
Mini 10
4 kg
Mini 11
Point-of-care
Mini 12
Mass Spectrometry:
the Science and Technology of Ions
Neutrals
$M_1, M_2, ..., M_n$
Soft Ionization
Ions
$m^{1+}, m^{2+}, ..., m^{n+}$
Mass Separation
m_p^+
$m_p^{1+}, m_p^{2+}, ...$
Mass Analysis
MS/MS Spectrum
MS/MS
Ions as Surrogates for Neutrals
Chemical Synthesis

Ionization Methods : Time Line

EI	CI	DI	SI	AI
Gases, vapors Electron impact	Gases, vapors Chemical ionization	Solids Desorption Ionization	Solutions Spray Ionization	Solids Solutions Ambient Ionization

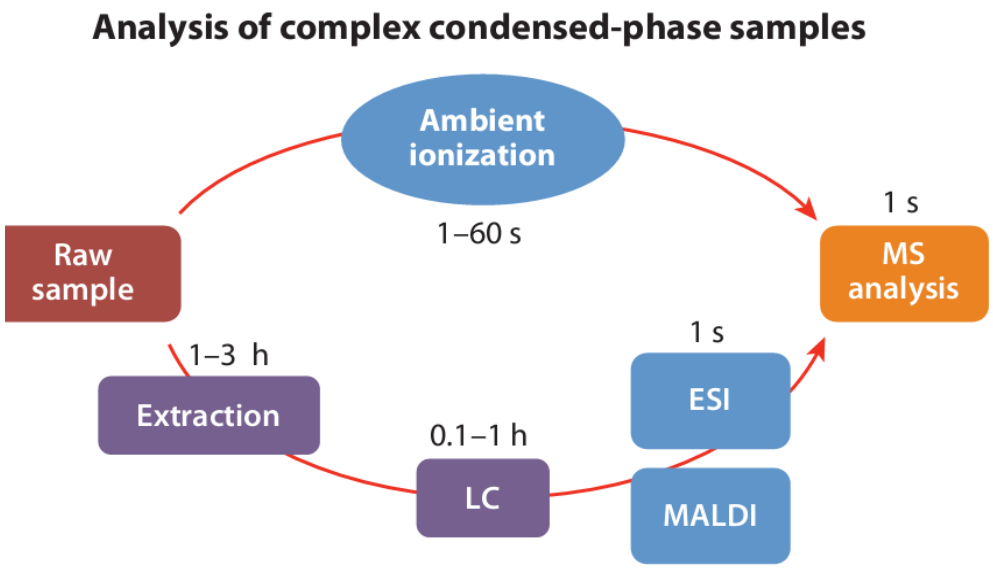


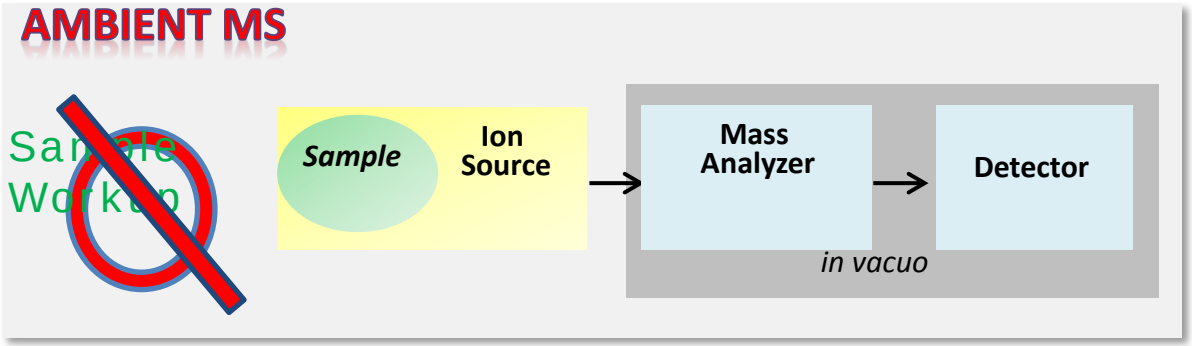
Ambient Ionization Mass Spectrometry

Ambient MS

- Direct analysis of ordinary objects in native environments
- Two processes....sampling and ionization
- No sample preparation
- Analyte ions - not whole sample - into MS
- Ionization in open environment

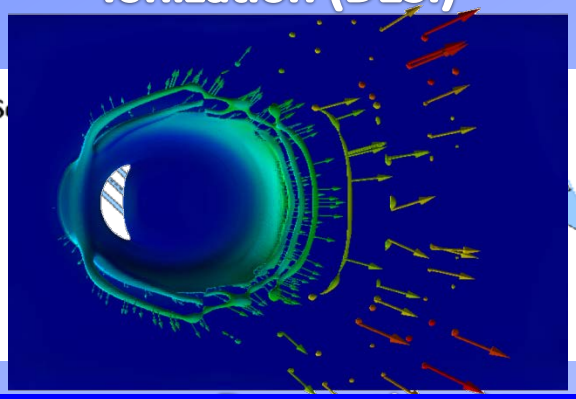
Timescale: Traditional vs. Direct Sampling and Ionization by Ambient Ionization MS



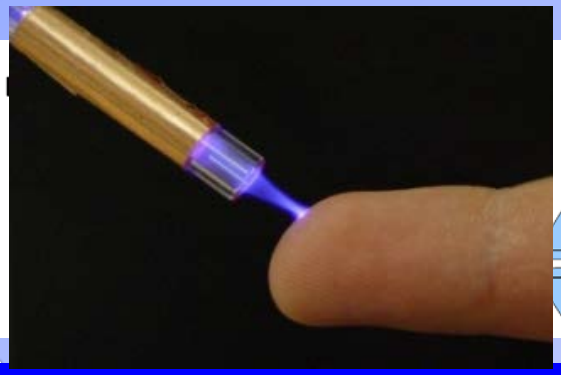


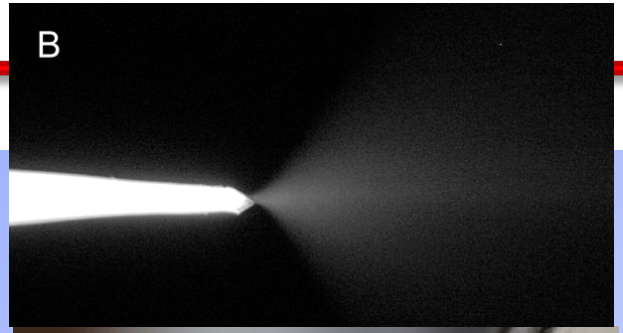
Ambient Ionization Methods

Desorption Electrospray Ionization (DESI)



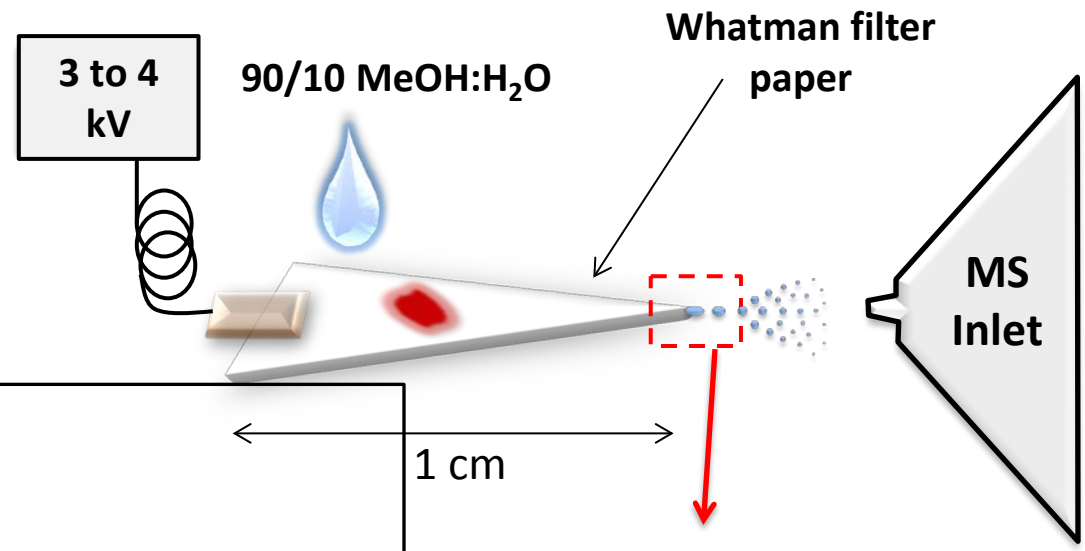
Low Temperature Plasma (LTP)

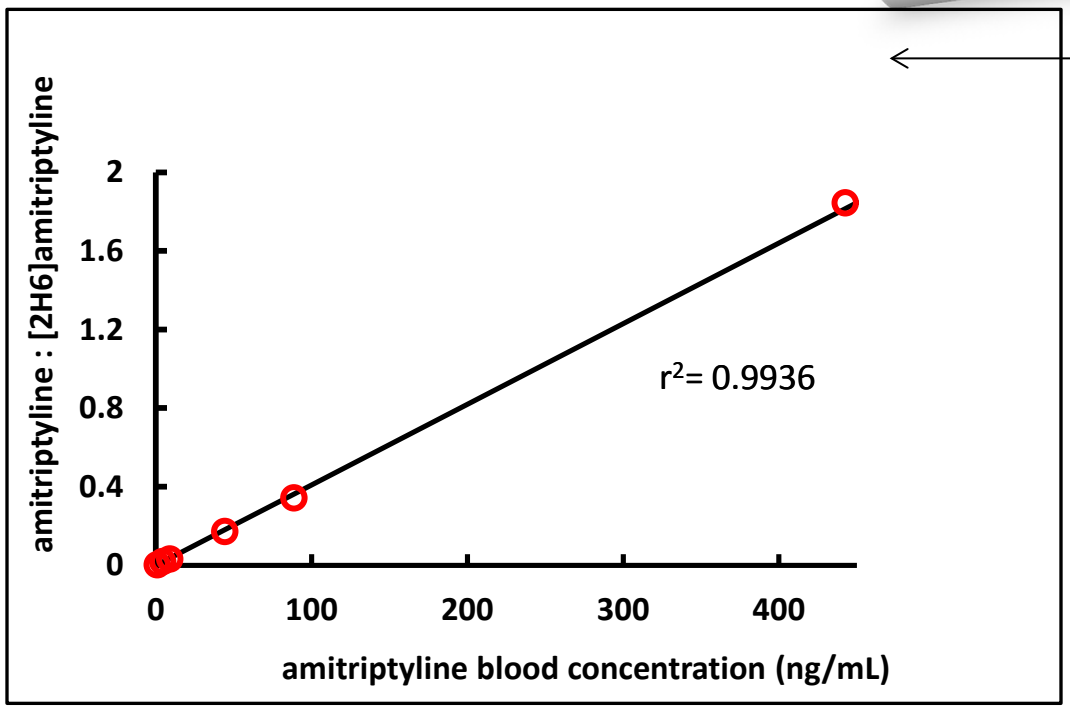


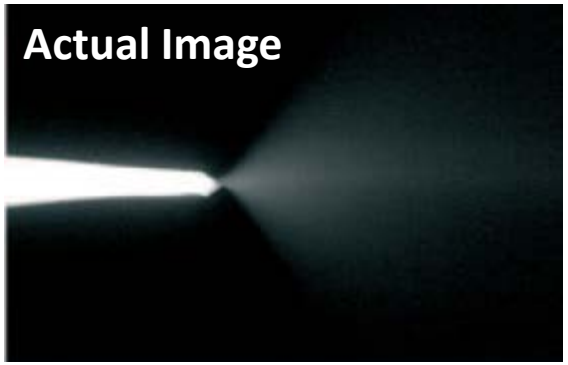


Point-of-Care Analysis

Paper Spray

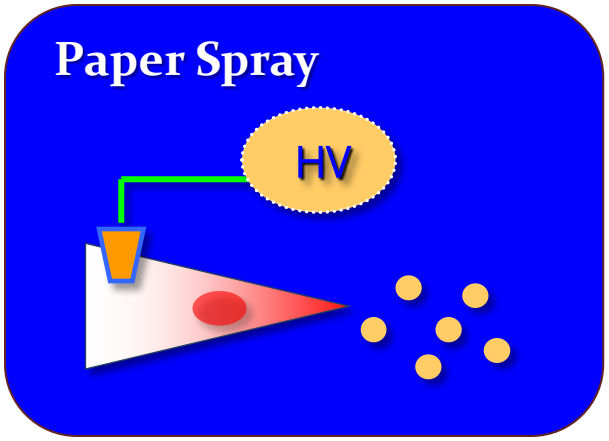


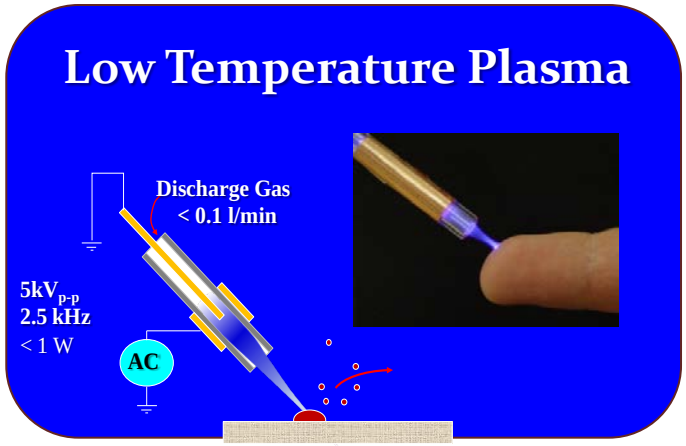


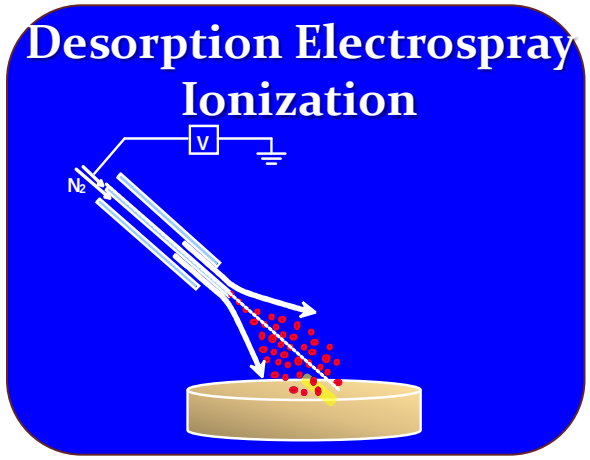


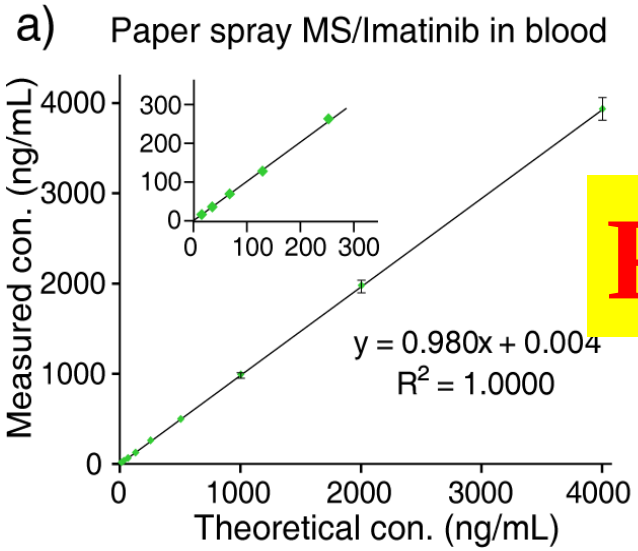
Wang, H.; Liu, J.; Cooks, R.G.; Ouyang, Z., *Angew. Chem. Int. Ed.* **2010**, 49, 877-880.
Liu, J.; Manicke, N.; Lin, J.; Cooks, R.G.; Ouyang, Z., *Anal. Chem.* **2010**, 82, 2463-2471.

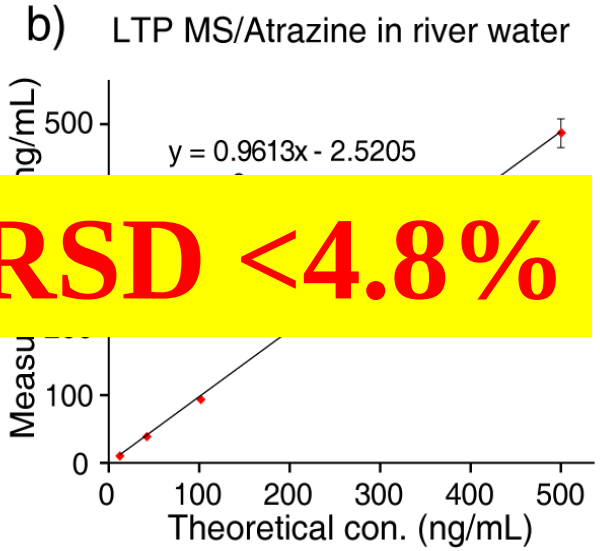
IS Coated Capillary Sampler – Making Ambient MS Quantitative

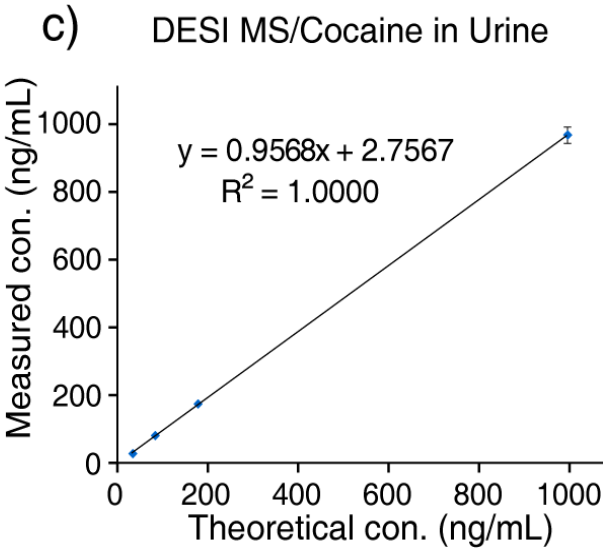












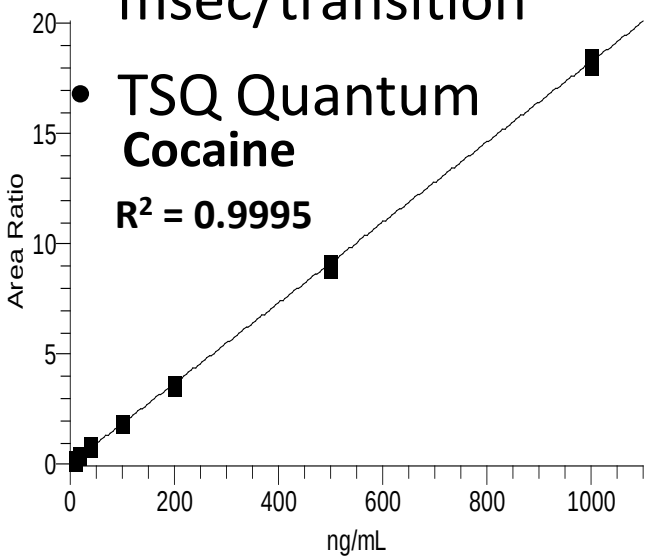
RSD <4.8%

J. Liu et al, AC 2013

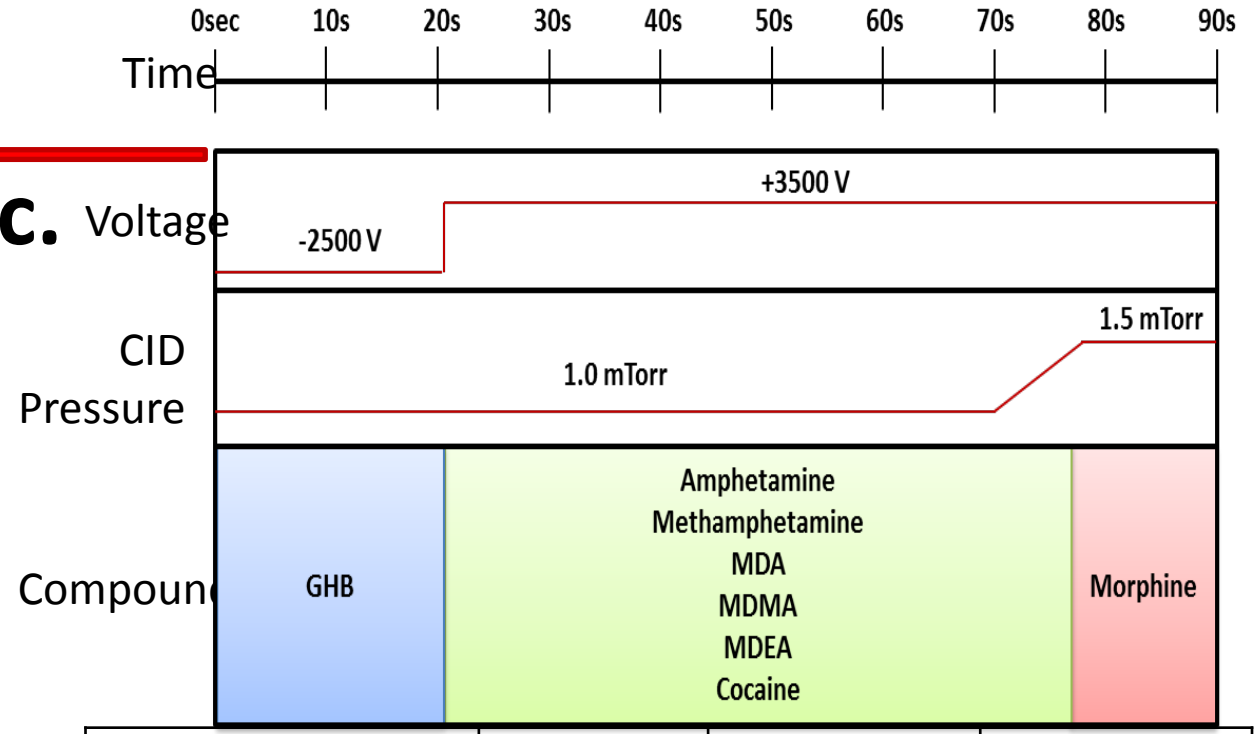
Paper Spray MS

9 Drugs in 90 sec.

- 3 injections of 5 µL solvent on top of 12 µL blood spot
- 20 SRM transitions per (analyte & int. std.) @ 75 msec/transition
- TSQ Quantum



Espy, Bas, van Asted, et al

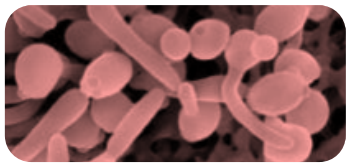


Compound	Cutoff (ng/mL)	LOD (ng/mL)	Calibration RSD's
Amphetamine	50	1.5	2-6 %
Methamphetamine		0.3	1-5 %
MDA		1.6	3-12 %
MDMA		0.04	1-11 %
MDEA		0.3	1-3 %
Cocaine		0.05	1-3 %
Morphine	20	12	1-10 %
GHB	10,000	78,000	3-14 %

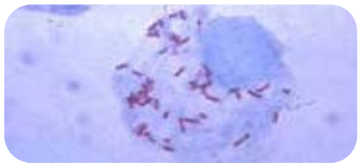
Touch Spray for Direct Microorganism Characterization

E. coli

C. albicans

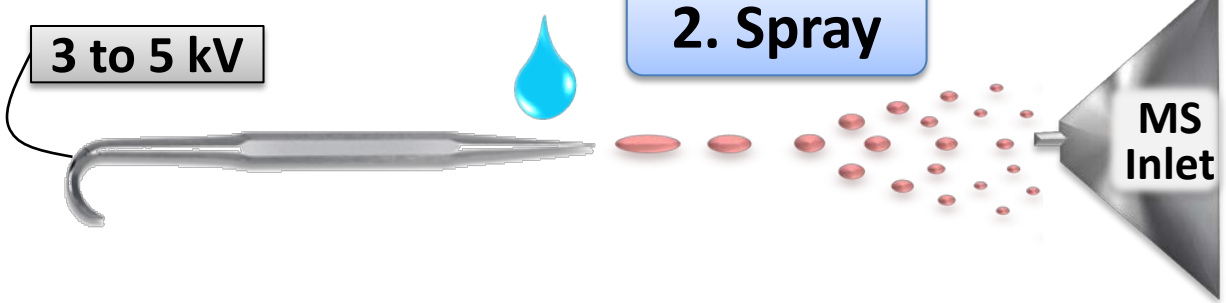


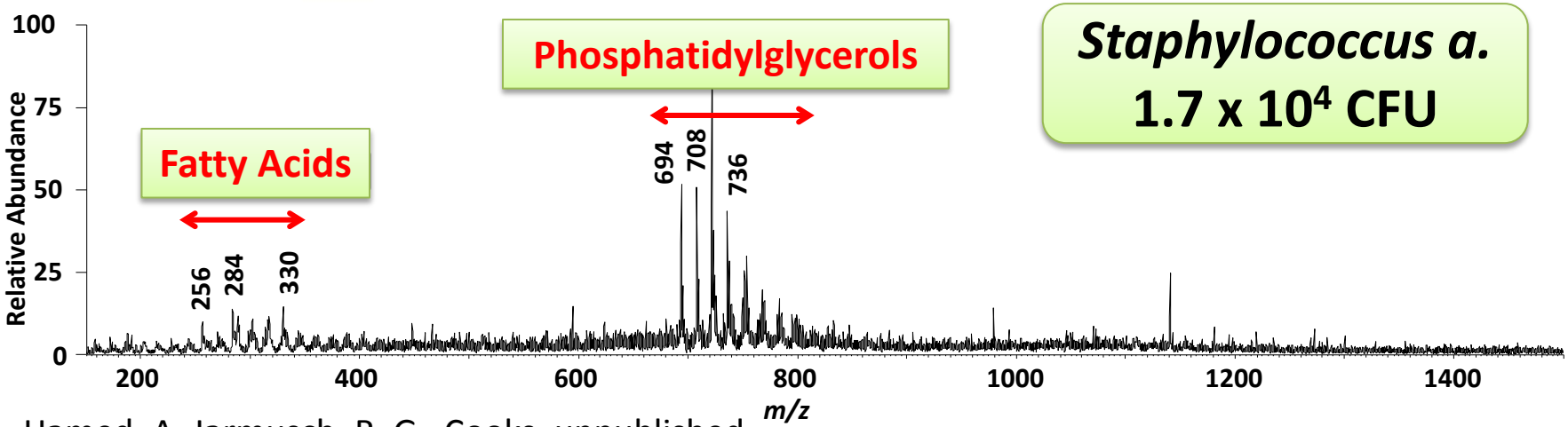
Rickettsia



- *Staphylococcus a.*
- *Salmonella*
- *C. botulinum*
- *M. tuberculosis*

1. Touch

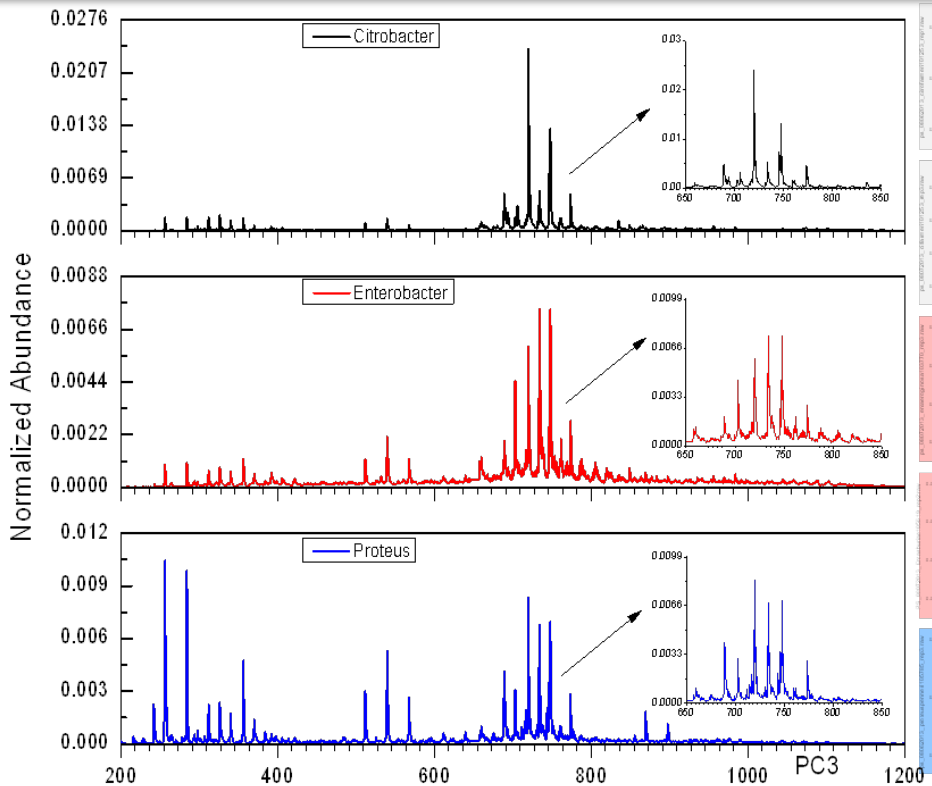


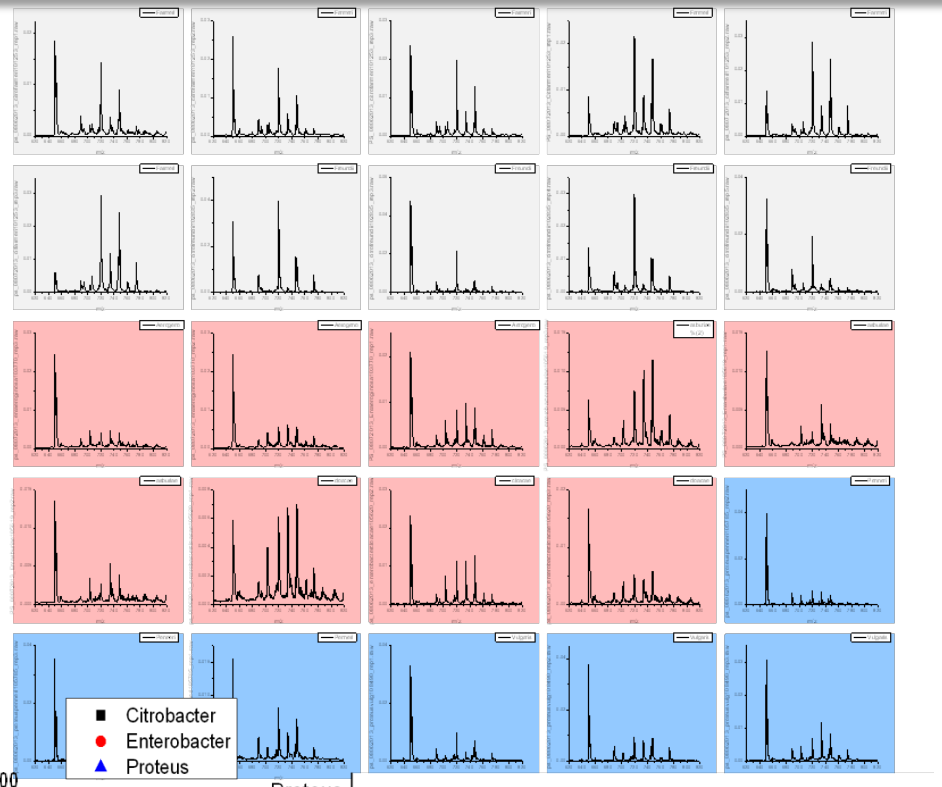


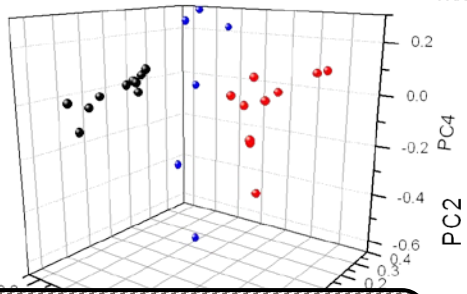
Staphylococcus a.
1.7×10^4 CFU

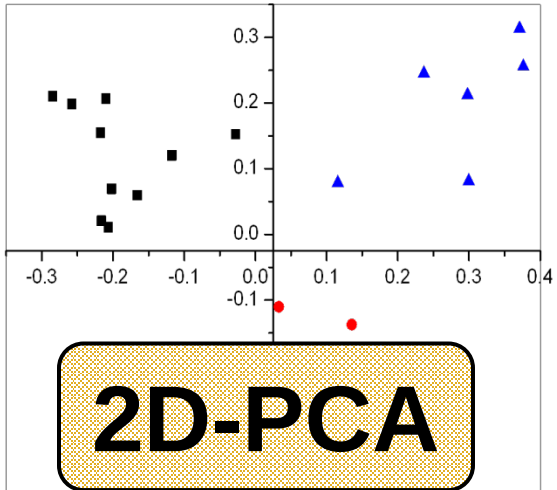
A. Hamed, A. Jarmusch, R. G. Cooks, unpublished

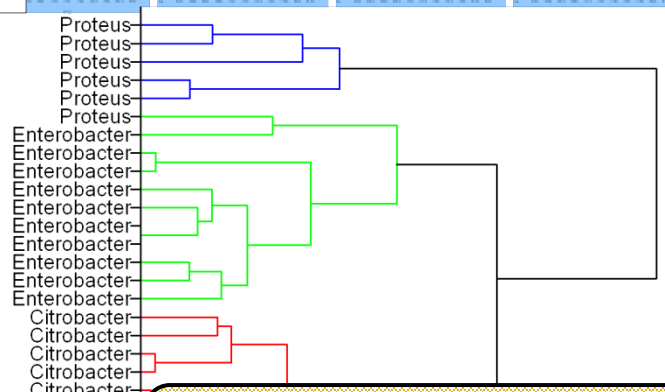
Genus Level Differentiation: Paper Spray









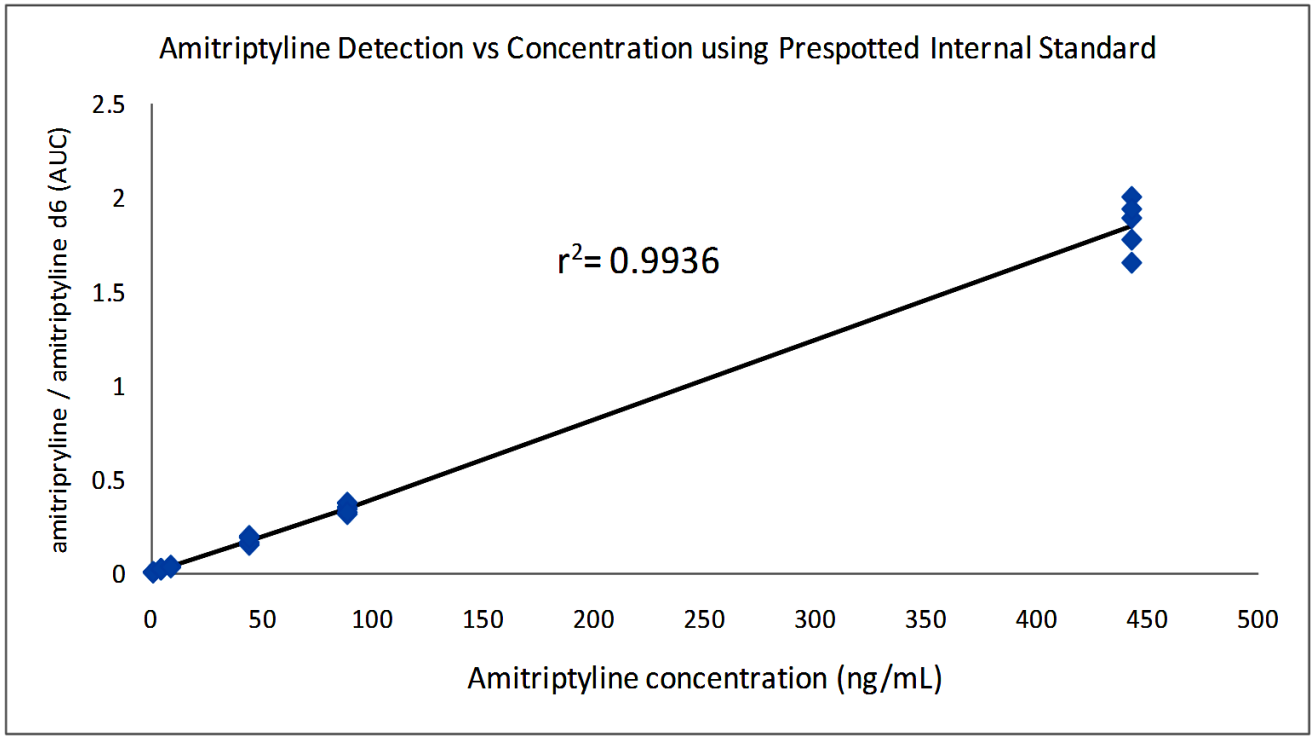


3D-PCA

2D-PCA

Dendrogram

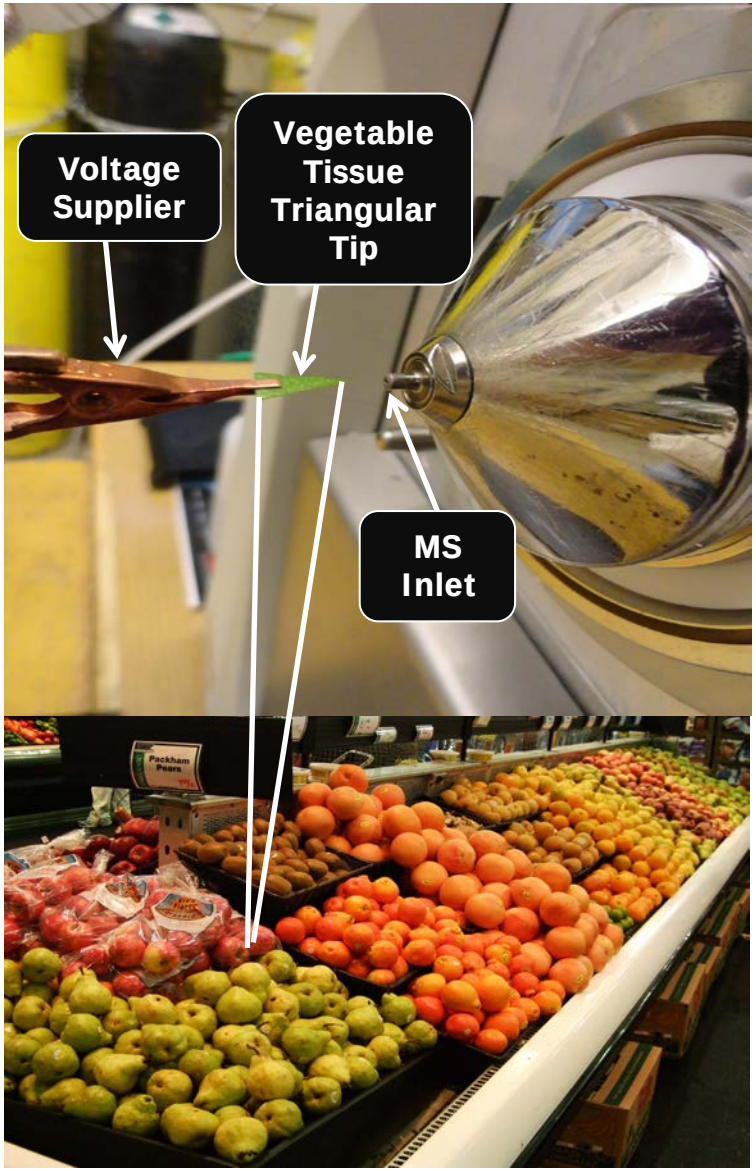
Paper Spray MS: Quantitation

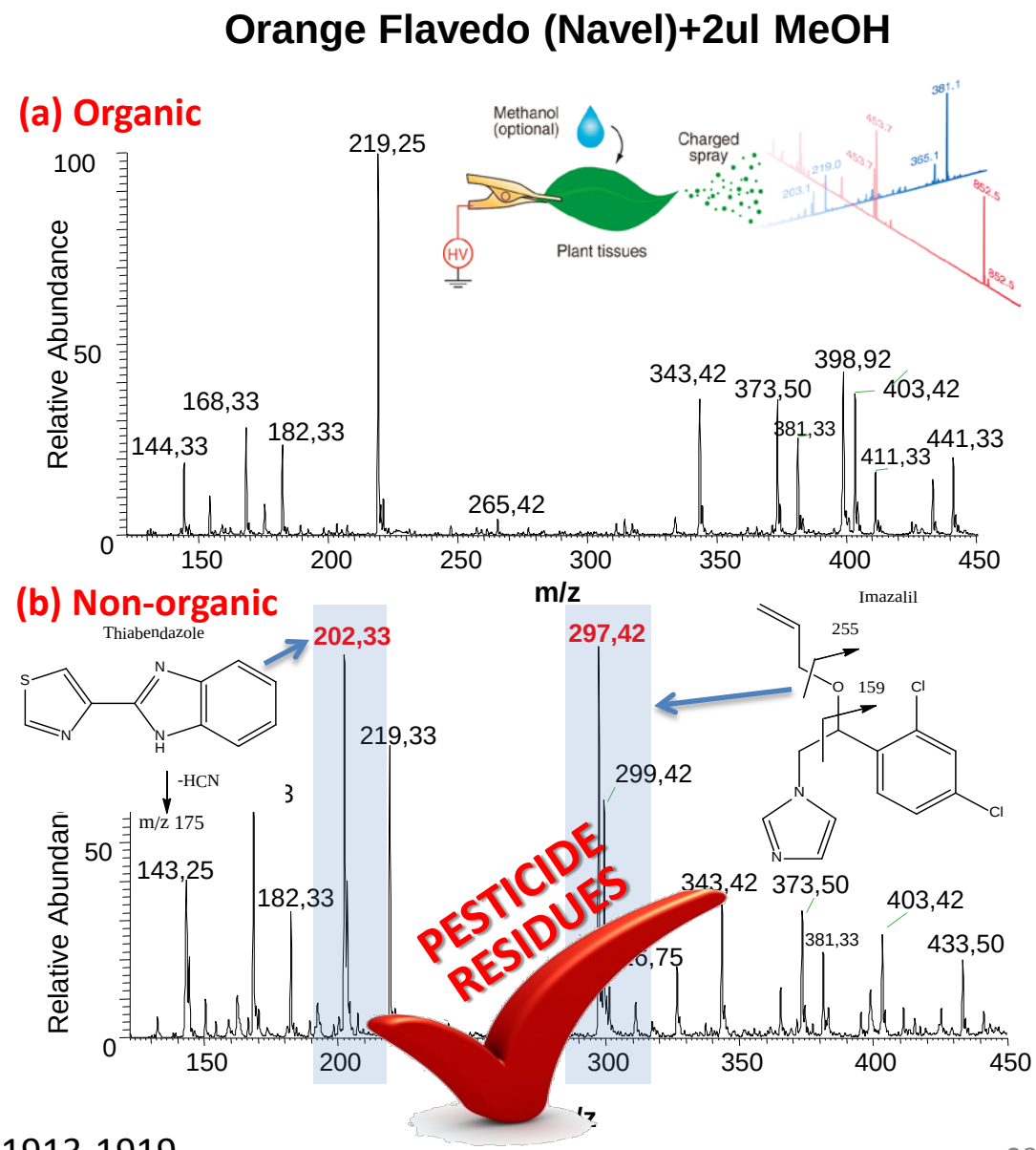


Prespotting internal standard onto the paper gives quantitative results

Actual concentration (ng/mL)	0.89	4.4	8.9	44	88
Average calculated concentration (ng/mL)	0.93	4.9	8.3	42	84
Imprecision (%CV)	22%	9%	10%	11%	7%
Accuracy (% bias)	5%	10%	-6%	-4%	-5%

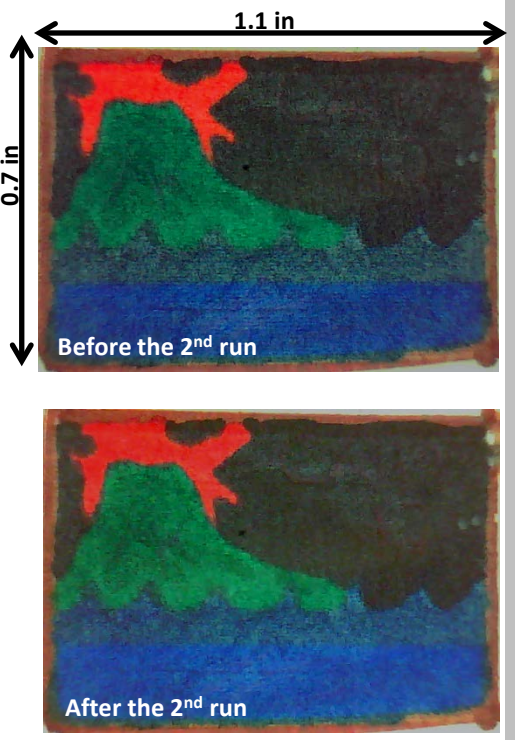
In Situ Analysis of Agrochemical Residues by Leaf Spray



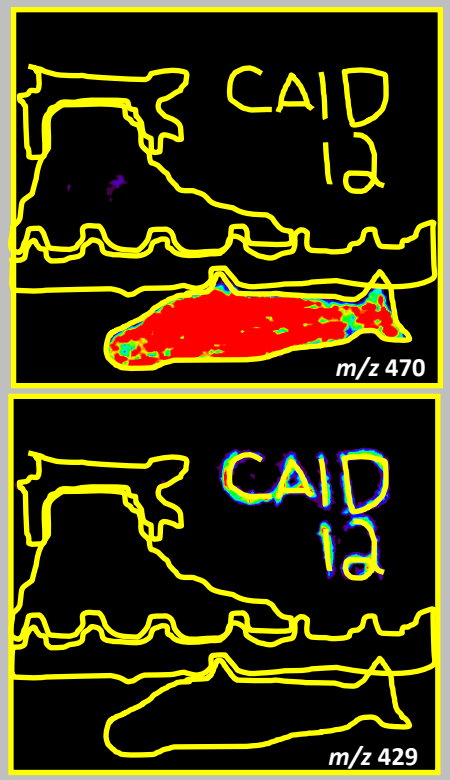


Naim Malaji, et al., *Anal. Methods*, 2012, 4, 1913-1919.

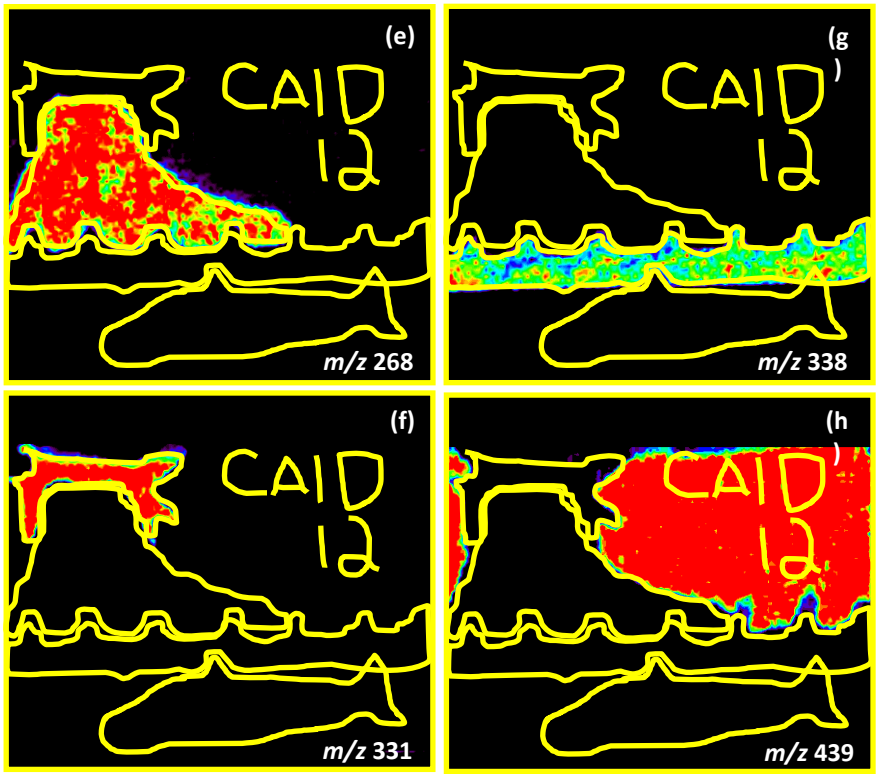
Hidden messages in paintings displayed by DESI-MS



2-year-old painting reanalyzed by DESI-MS imaging



The shark and the text are not visible in the painting



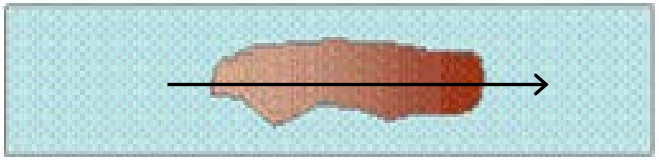
Each element in the painting (volcano, lava, sky, waves) shows characteristic ion images

- *Art painting conservation analysis*
- *Non-destructive*
- *Molecular mapping adds information not detectable by analysis*

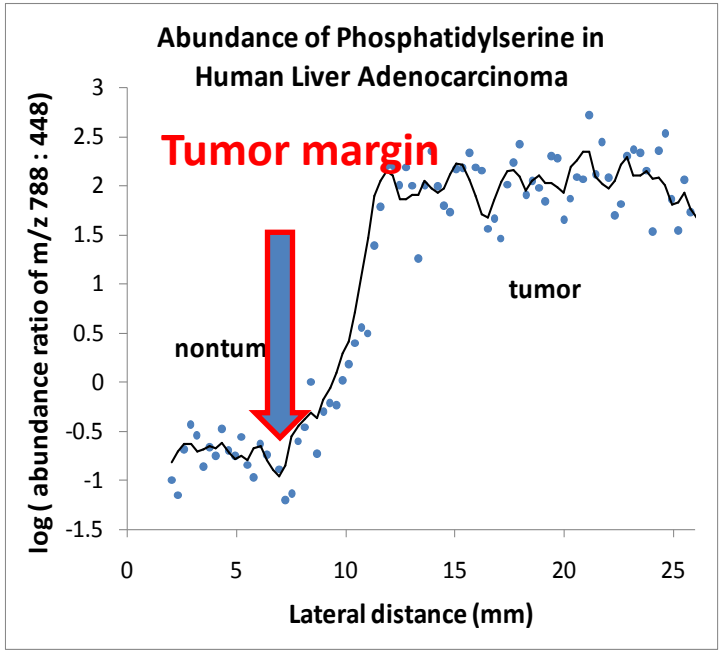
Images

Tissue Analysis : Metabolite Profiling

a) Line Scans



Signal ratios from MS



b) Tissue Imaging

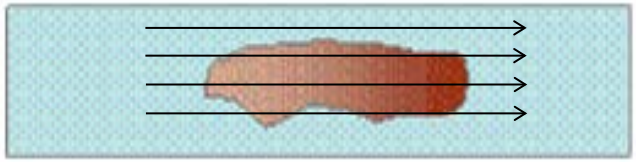
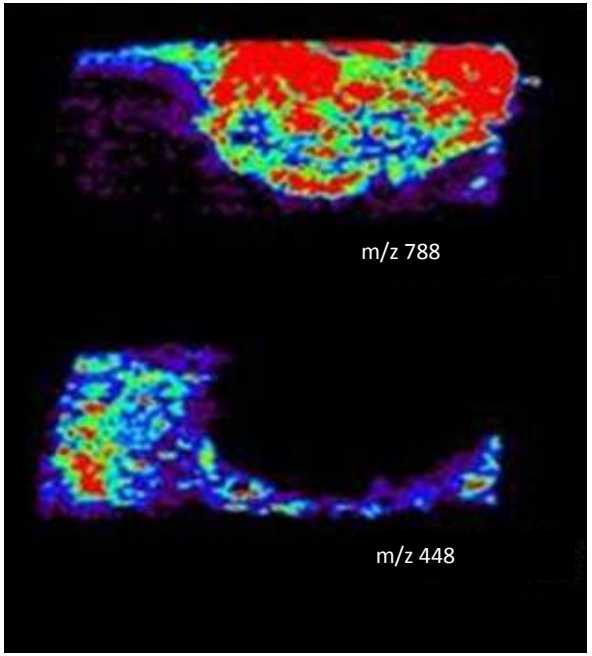


Image construction



Justin M. Wiseman, Satu M. Puolitaival, Zoltán Takáts, R. Graham Cooks, Richard M. Caprioli, *Angew. Chem*. 2005

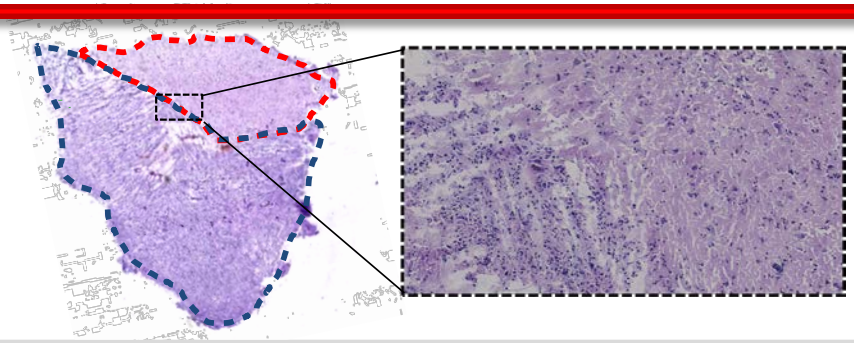
Human Brain Cancers

- Over 125 types of brain tumors – complex to diagnose
- Mean survival 12 – 15 months to some years
- New cases (US): 22,910/year, deaths: 13,700/year
- Neurosurgery is the primary treatment
- Critical decisions made during neurosurgery

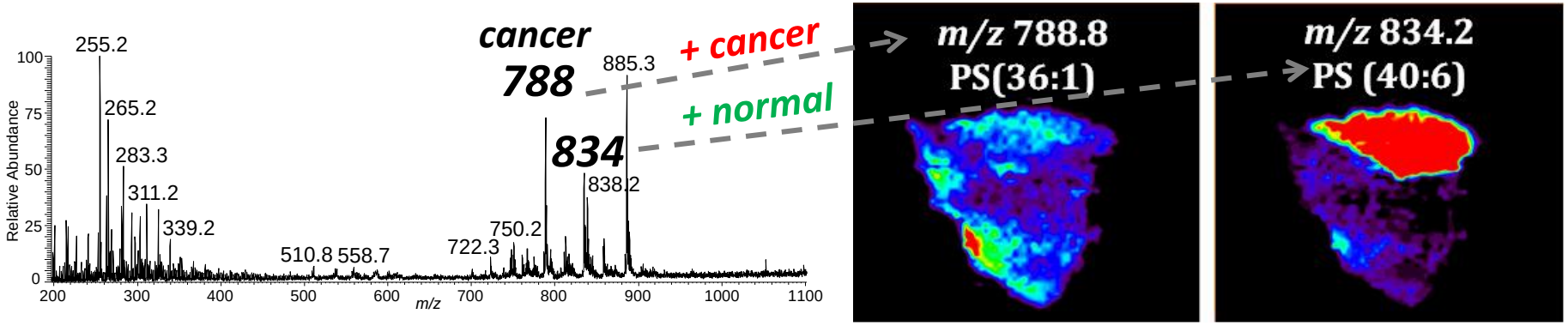
Need: Improved intraoperative diagnosis of tumors & margins One Answer: Direct tissue analysis! – Molecular histology using Mass Spec

Human Brain Cancers

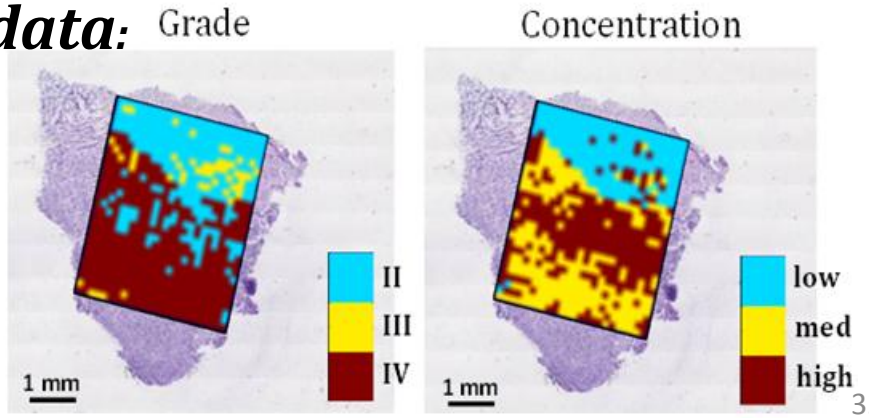
1. *What the pathologist sees :*



2. *MS -- distribution of hundreds of chemicals:*



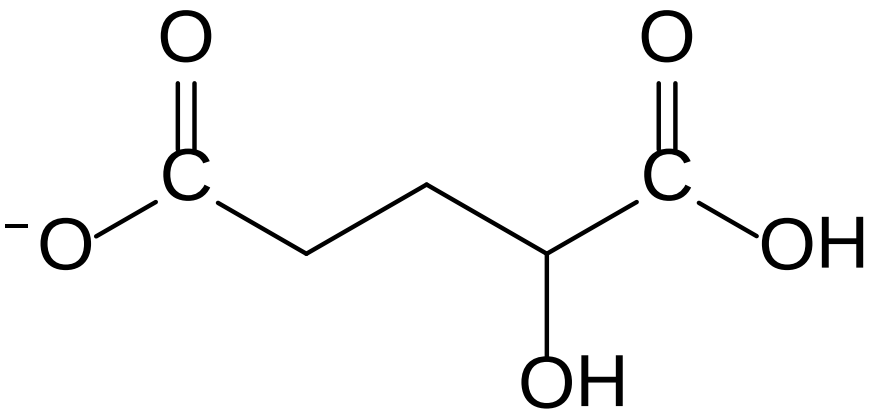
3. *Automatic interpretation of MS data:*



L.S. Eberlin, I. Norton, et al *Cancer Research*, **2012**, 72, 645

Lipid Metabolites for Disease Diagnosis & Prognosis

2- HG 2-hydroxyglutarate



m/z 147

- **Recurrent mutations in genes encoding iso[illegible]dehydrogenase I and II {IDH1/2)**
- **Occur in gliomas and other tumor type[illegible]**
- **Mutant enzymes convert 1-ketoglu[illegible] 2-hydroxyglutarate (2-HG)**
- **2-HG positive tumors have imp[illegible]utcome**
- **Oncometabolite 2-HG in tu[illegible] 100's ug/g levels - assayed by MRI**
- **DESI MS imaging during [illegible], w/o sample preparation**

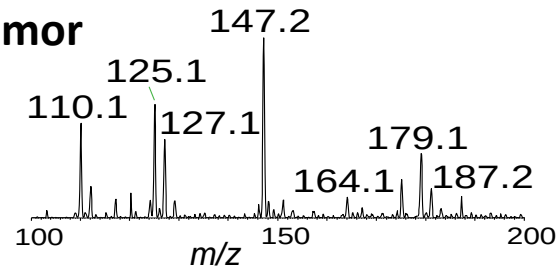
MS in operating suite

Metabolite-imaging mass spectrometry to guide brain surgery [Purdue University, Harvard Medical School]

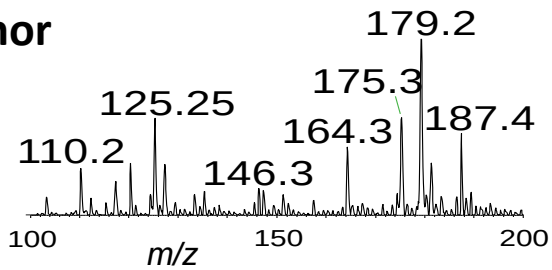
Sandro Santagata, Livia S. Eberlin, Isaiah Norton, Jennifer L. Ide, Daniel R. Feldman, Xiaohui Liu, Joshua S. Wiley, Shakti Ramkissoon, Daniel A. Orringer, Kristen K. Gill, Ian F. Dunn, Dora Dias-Santagata, Keith L. Ligon, Ferenc A. Jolesz, Alexandra J. Golby, R. Graham Cooks and Nathalie Y.R. Agar, unpublished

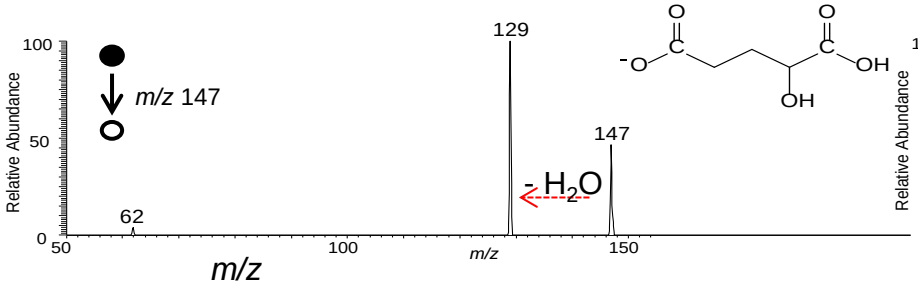
Metabolite-imaging MS to guide brain surgery

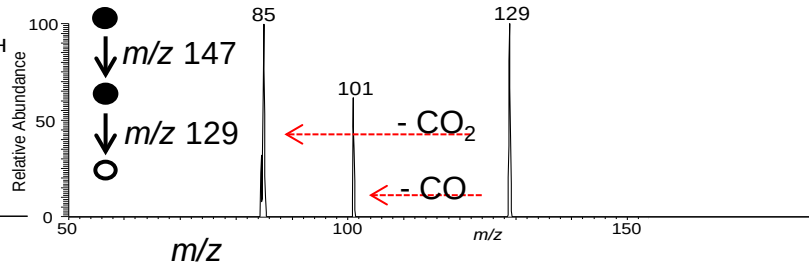
2-HG pos. tumor

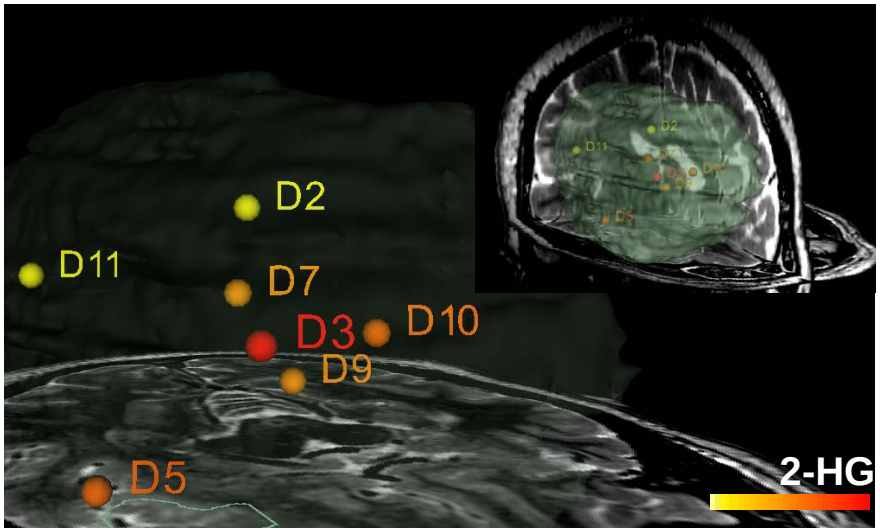


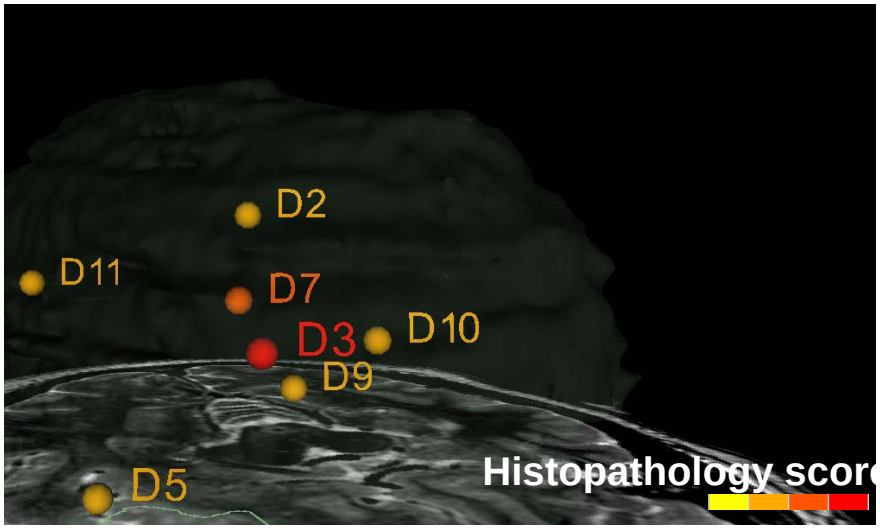
2-HG neg. tumor



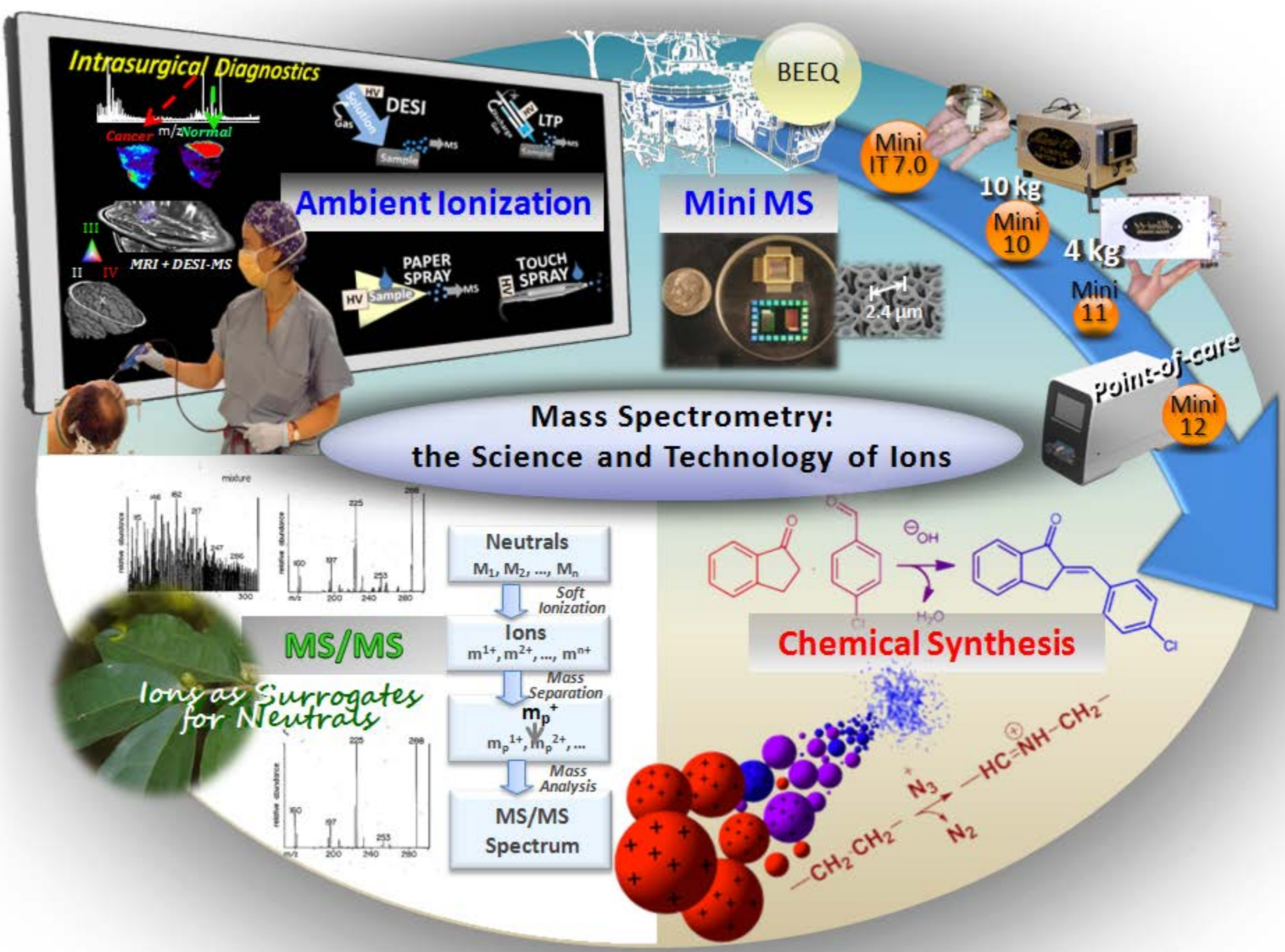




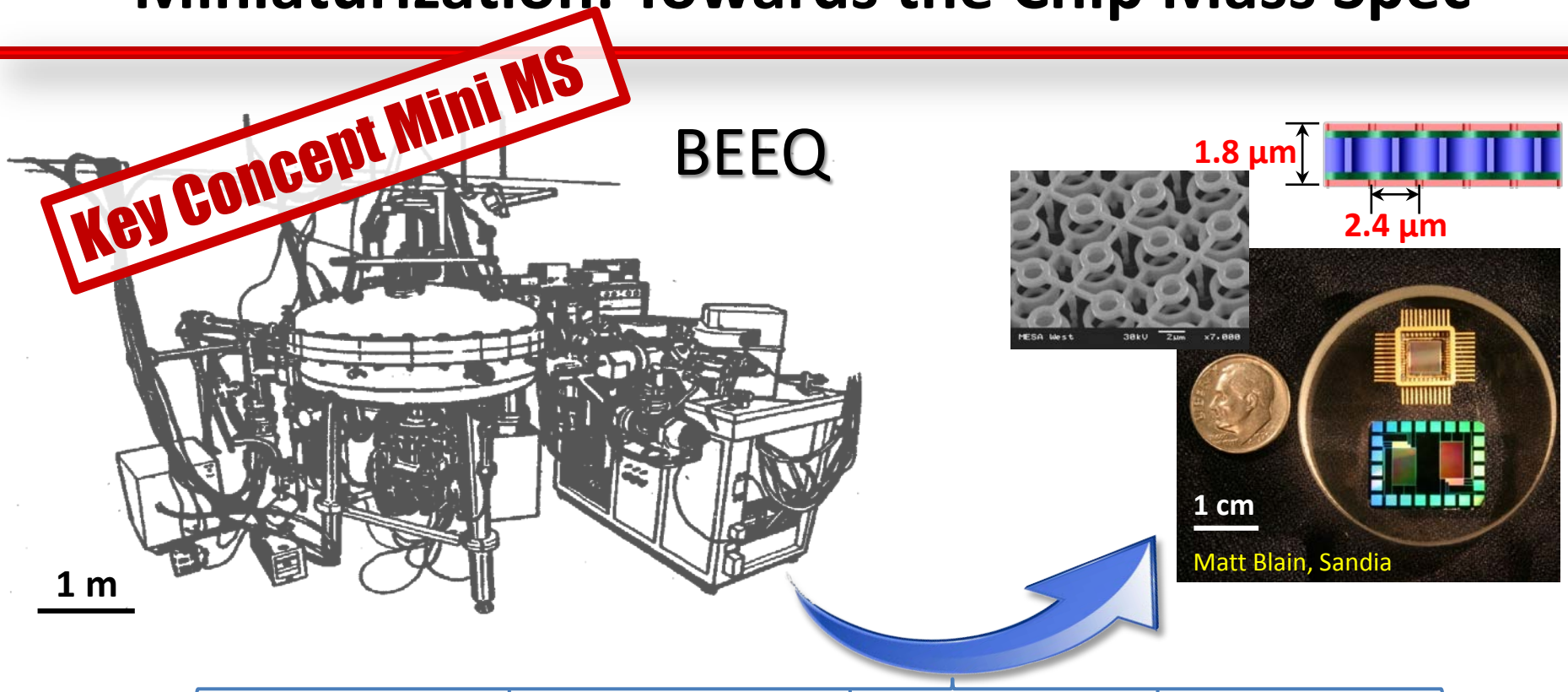




Sandro Santagata, Livia S. Eberlin, Isaiah Norton, Jennifer L. Ide, Daniel R. Feldman, Xiaohui Liu, Joshua S. Wiley, Shakti Ramkissoon, Daniel A. Orringer, Kristen K. Gill, Ian F. Dunn, Dora Dias-Santagata, Keith L. Ligon, Ferenc A. Jolesz, Alexandra J. Golby, R. Graham Cooks and Nathalie Y.R. Agar, unpublished


Intrasurgical Diagnostics
Cancer
m/z
Normal
MRI + DESI-MS
DESI
LTP
Ambient Ionization
PAPER SPRAY
TOUCH SPRAY
BEEQ
Mini MS
2.4 µm
Mini IT 7.0
10 kg
Mini 10
4 kg
Mini 11
Point-of-care
Mini 12
Mass Spectrometry:
the Science and Technology of Ions
Neutrals
$M_1, M_2, ..., M_n$
Soft Ionization
Ions
$m^{1+}, m^{2+}, ..., m^{n+}$
Mass Separation
m_p^+
$m_p^{1+}, m_p^{2+}, ...$
Mass Analysis
MS/MS Spectrum
MS/MS
Ions as Surrogates for Neutrals
Chemical Synthesis

Miniaturization: Towards the Chip Mass Spec

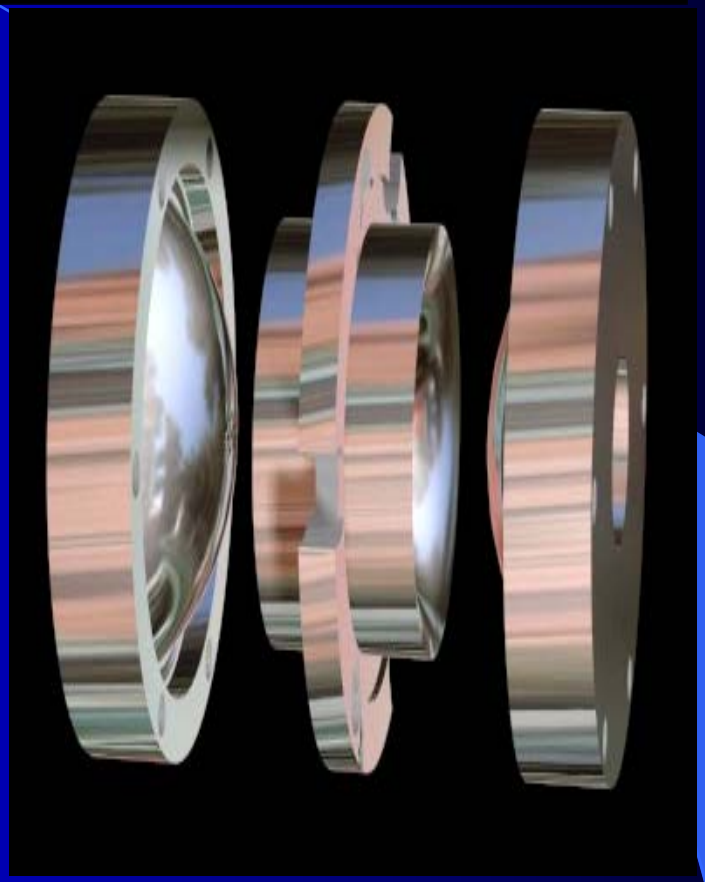


Paul Ion Trap

$$\frac{d^2u}{d\xi^2} + a_u - 2q_u \cos 2\xi \, u = 0$$

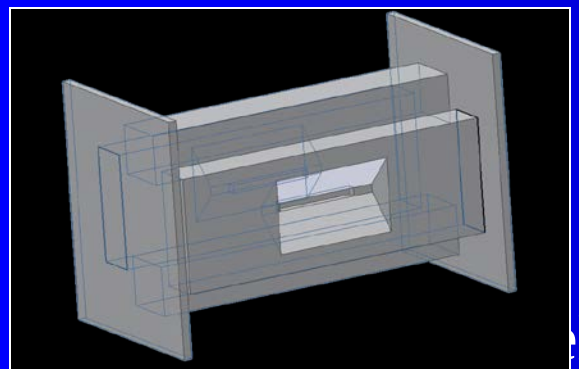
Wolfgang Paul

Nobel Prize 1989



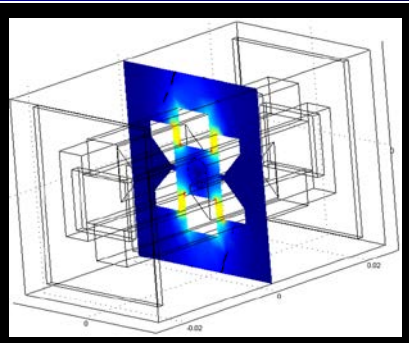
Quadrupole Ion Trap

Ion Trap Simulation Procedures



Mechanical Modeling
Inventor, SolidWorks

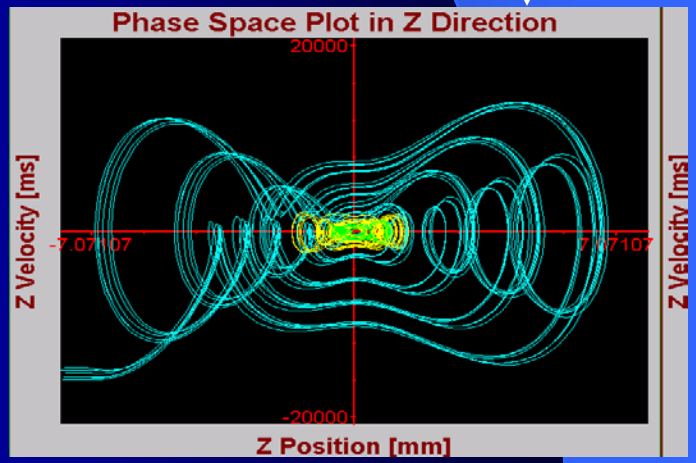
3D field solver
(HFSS, FEMLAB)



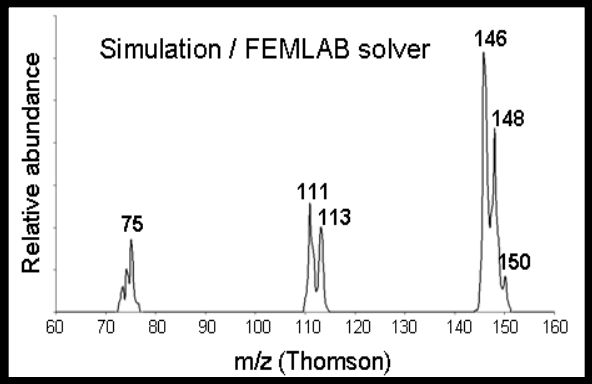
Field Solving:
POISSON, FEMLAB, HFSS

E_x, E_y, E_z files

3D Ion Trajectory
SIMulation (ITSIM)

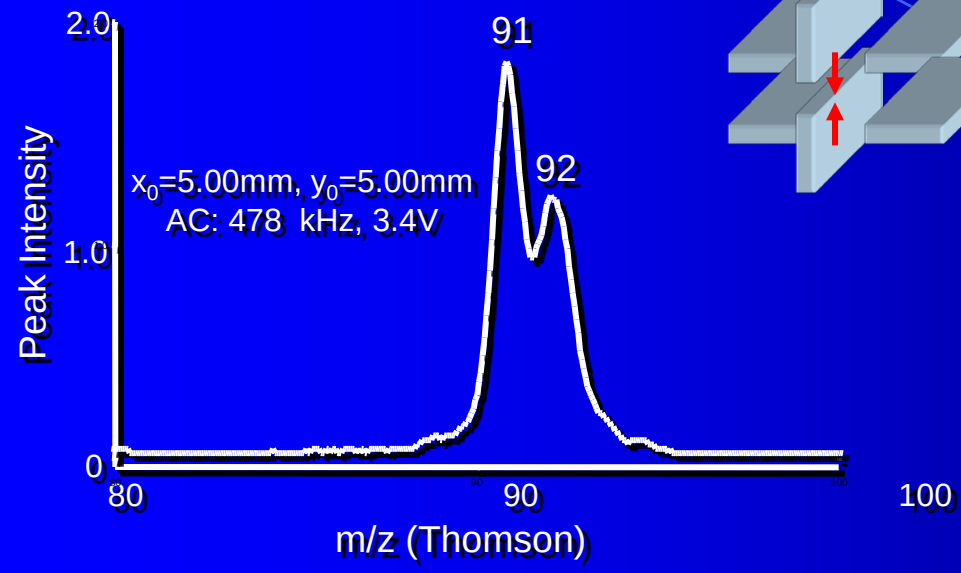


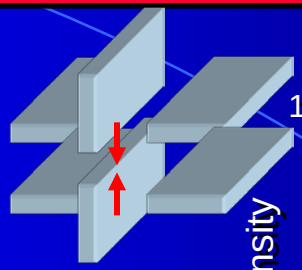
Stability Diagrams
Design Guidelines

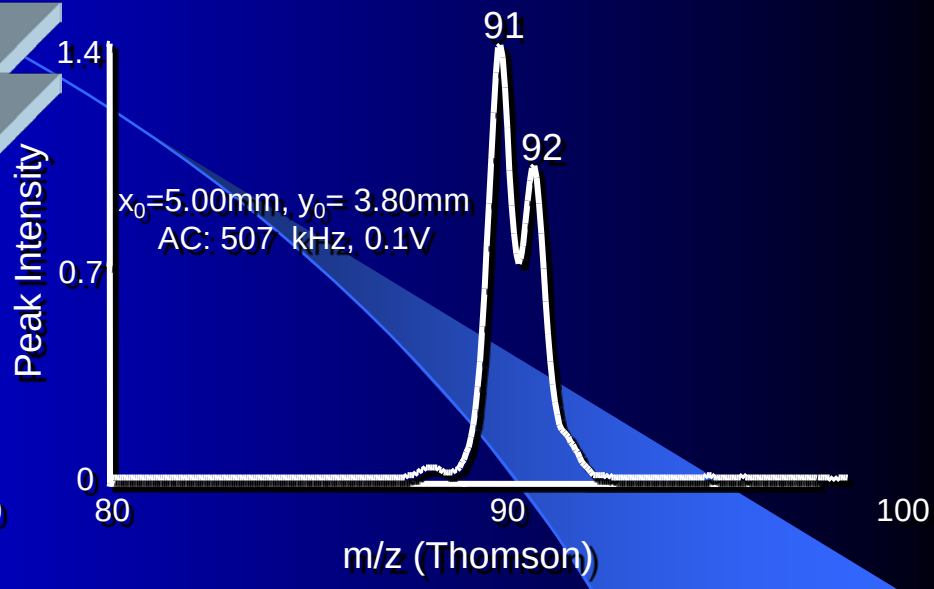


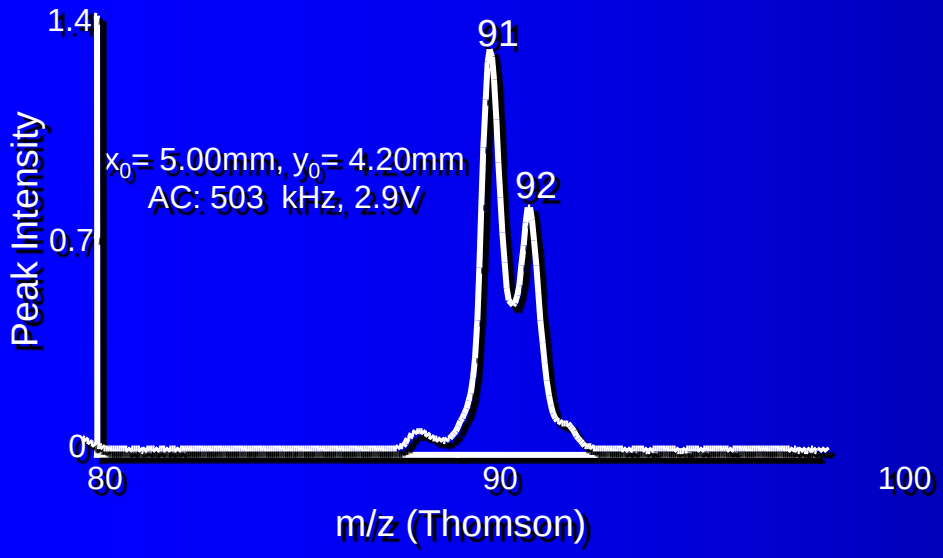
Prototype
Revision

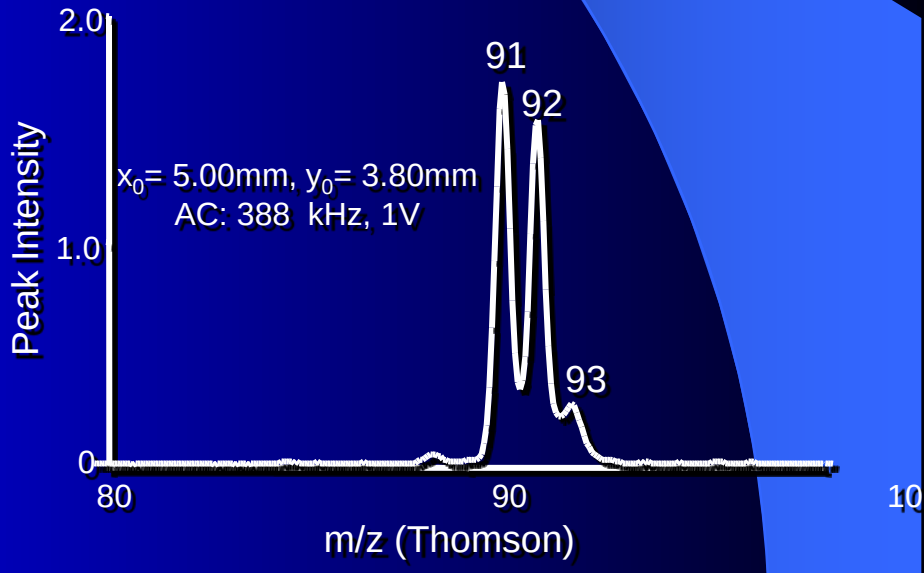
Optimization to the Geometry of RIT







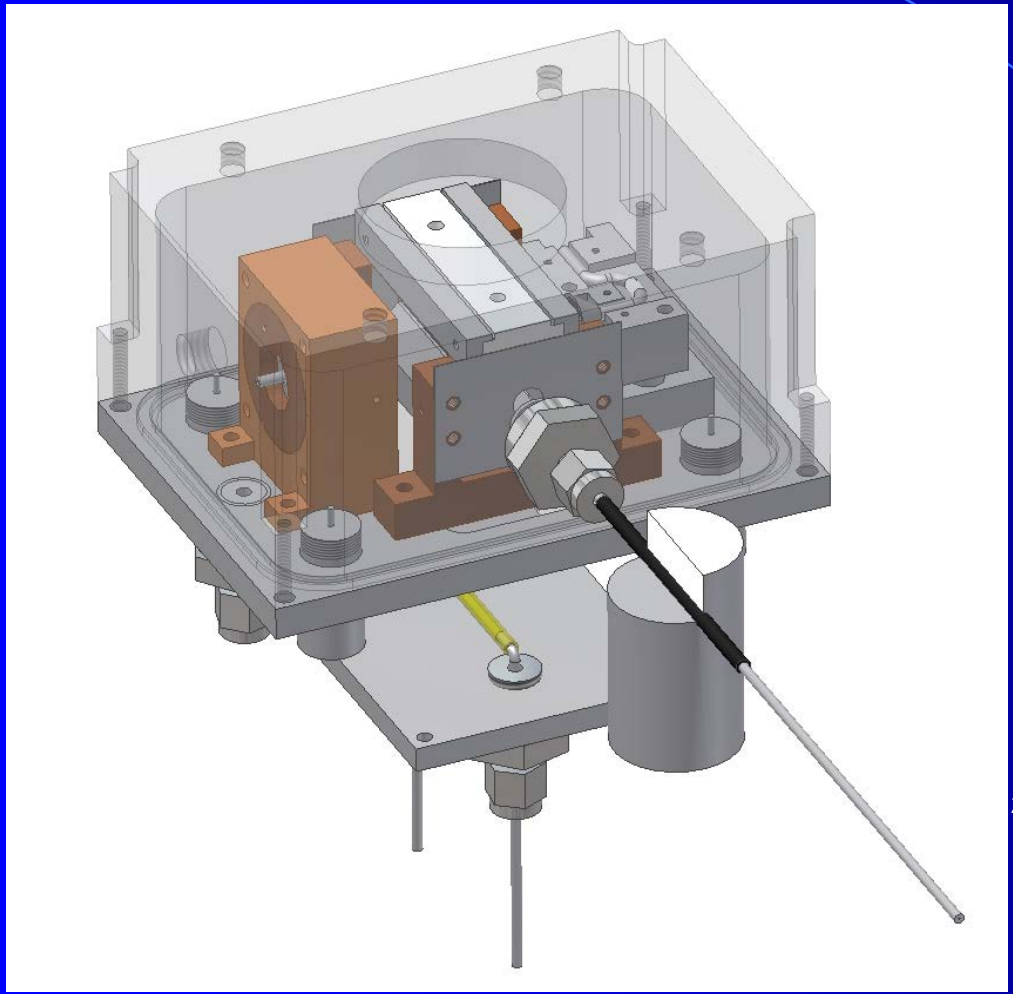


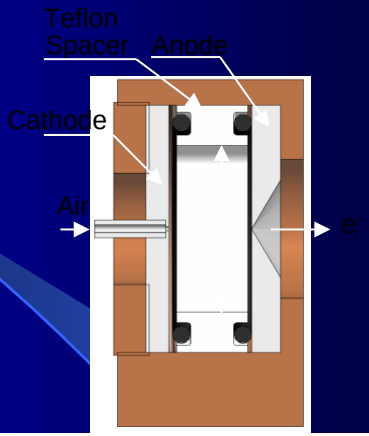


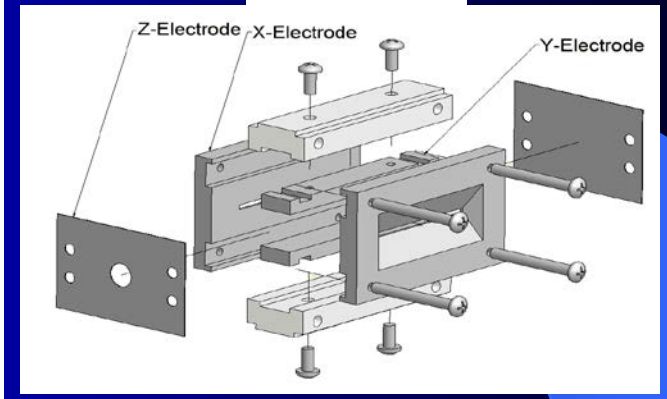
Mini 11 Mass Analyzer

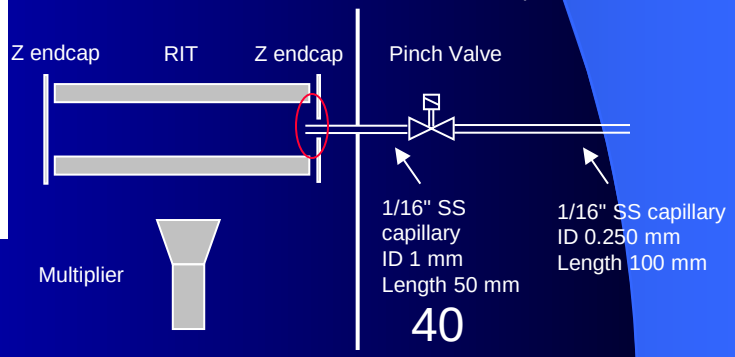
Manifold

GDEI

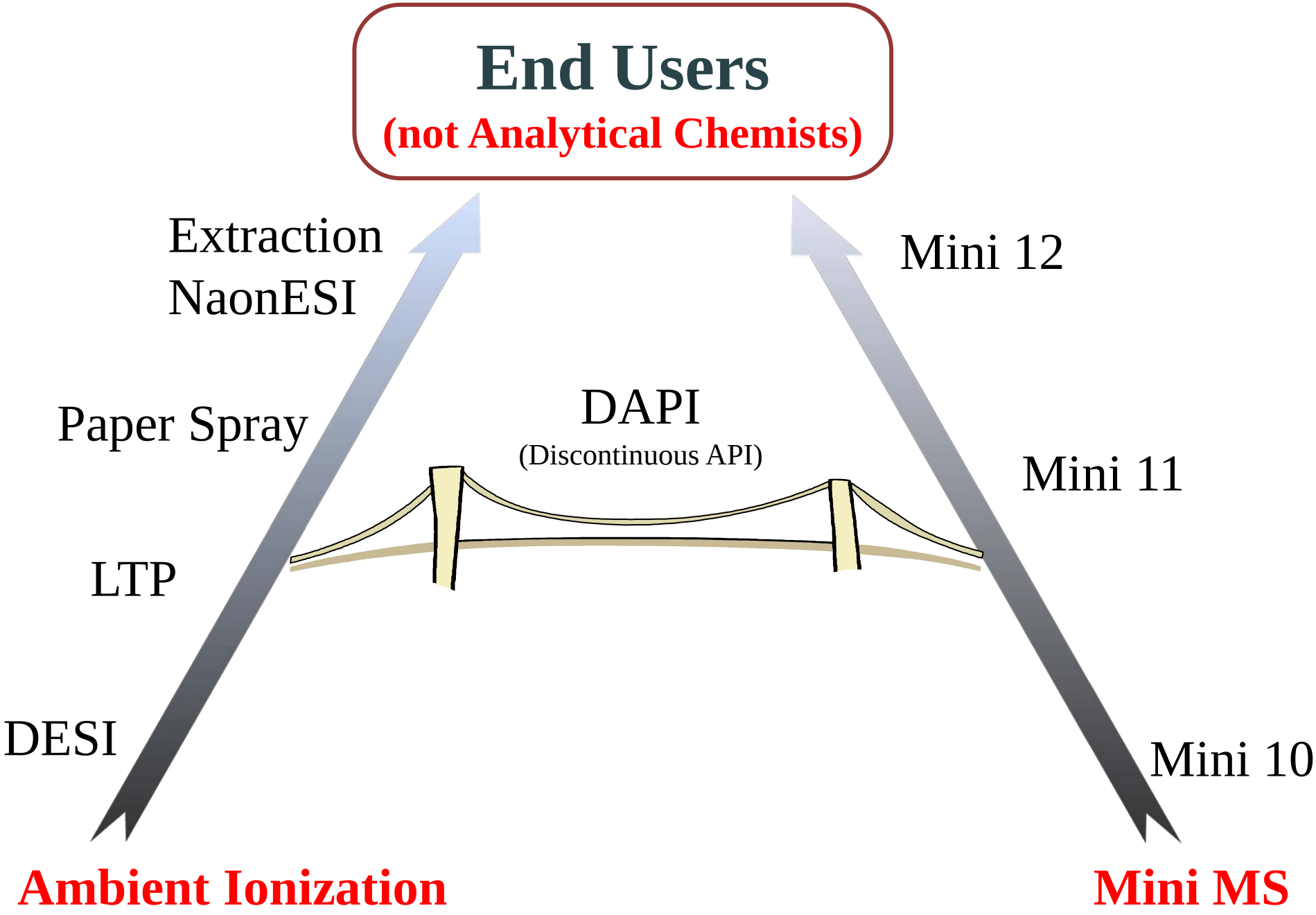








Constant z electrodes voltage


End Users
(not Analytical Chemists)
Extraction
NaonESI
Paper Spray
LTP
DESI
DAPI
(Discontinuous API)
Mini 12
Mini 11
Mini 10
Ambient Ionization
Mini MS

Miniaturization of Pumping System

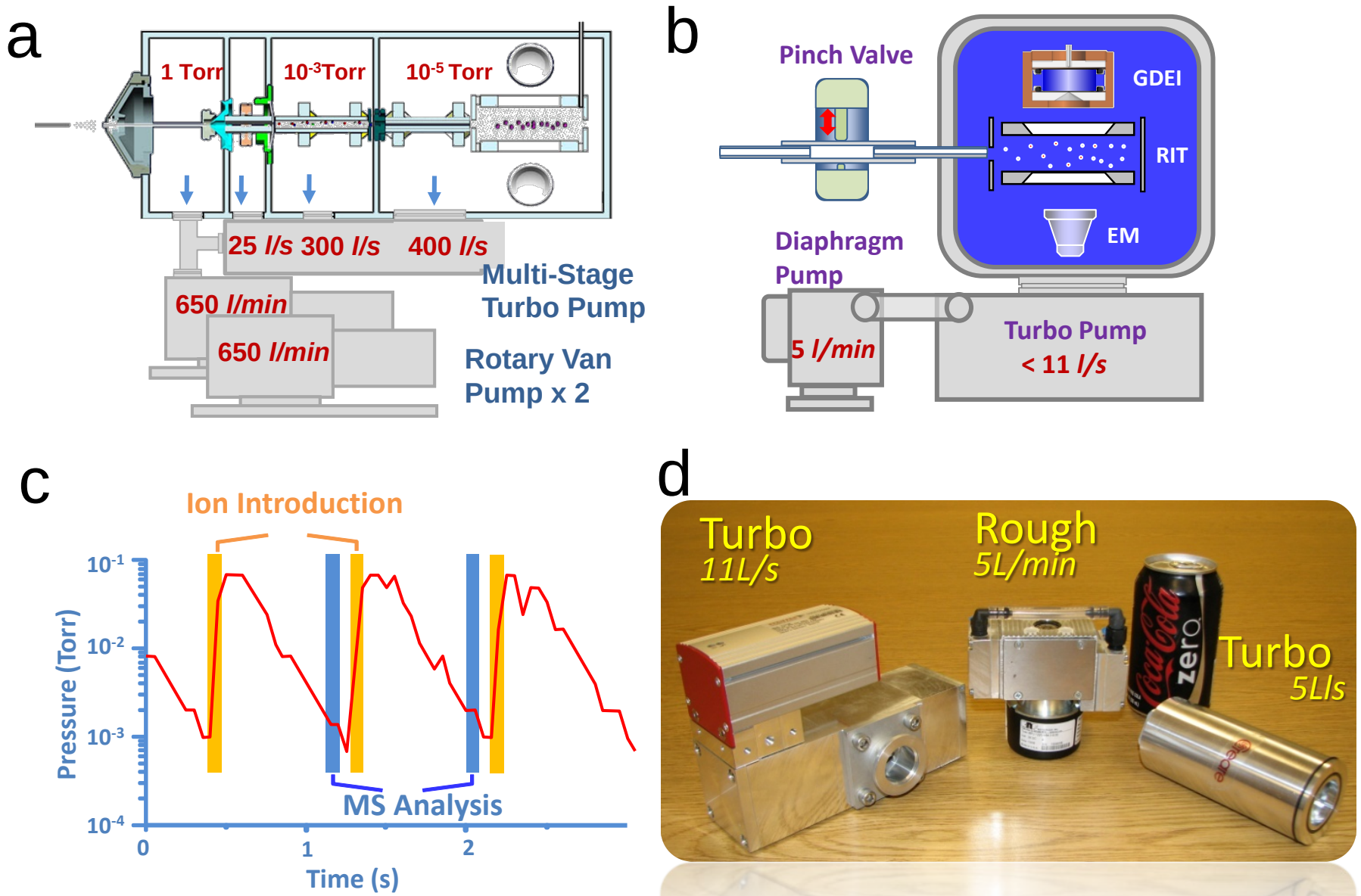
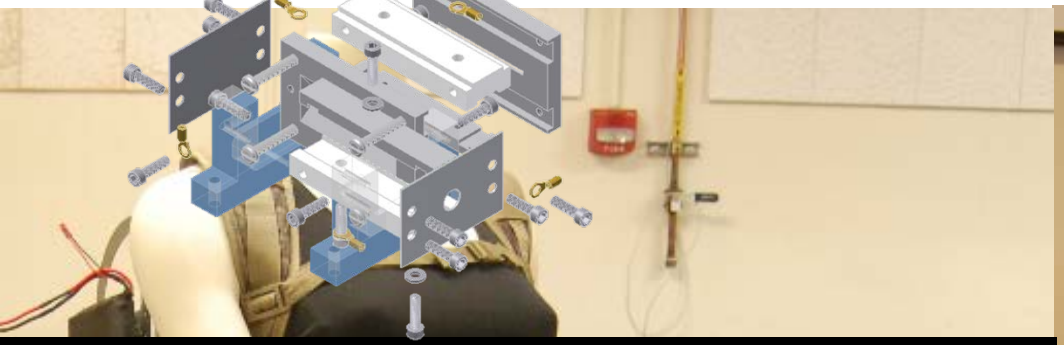
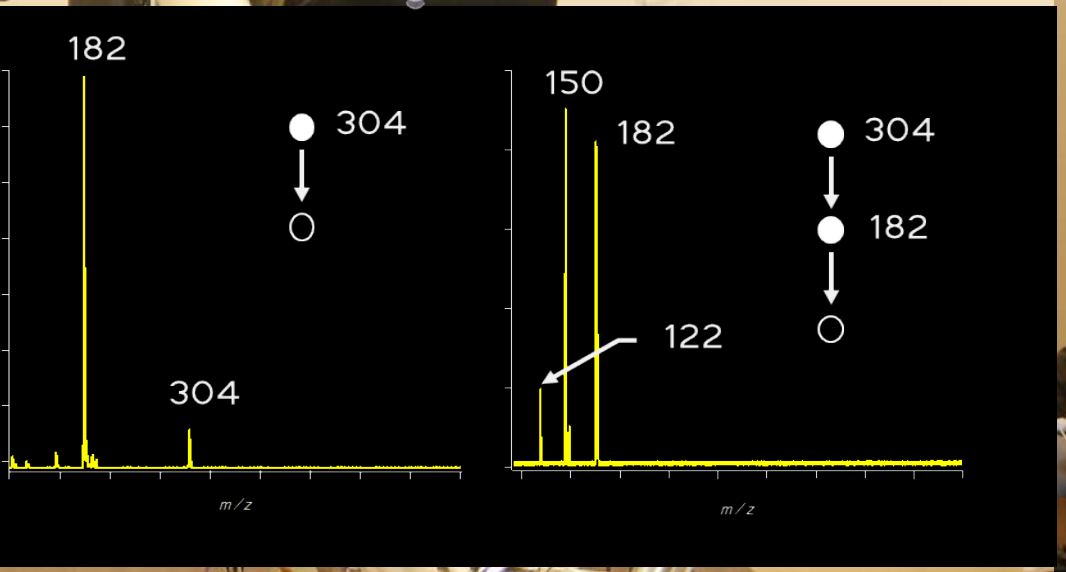
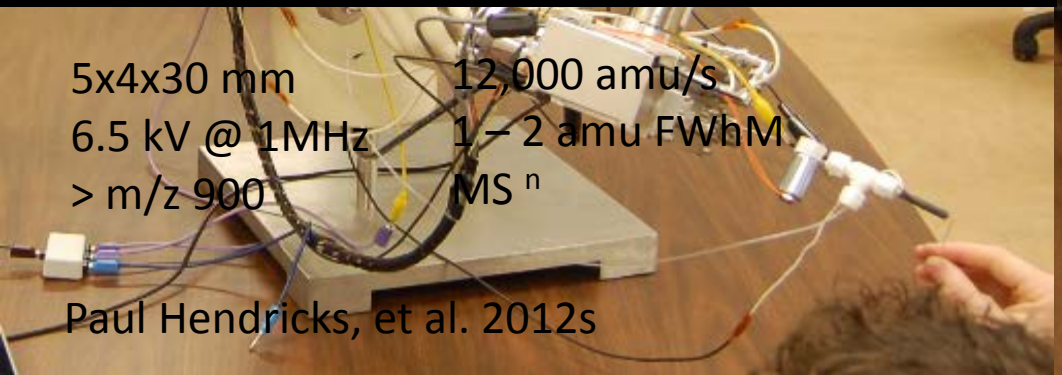


Figure 12

Backpack MS with Handheld LTP Sampling Probe Mini 12



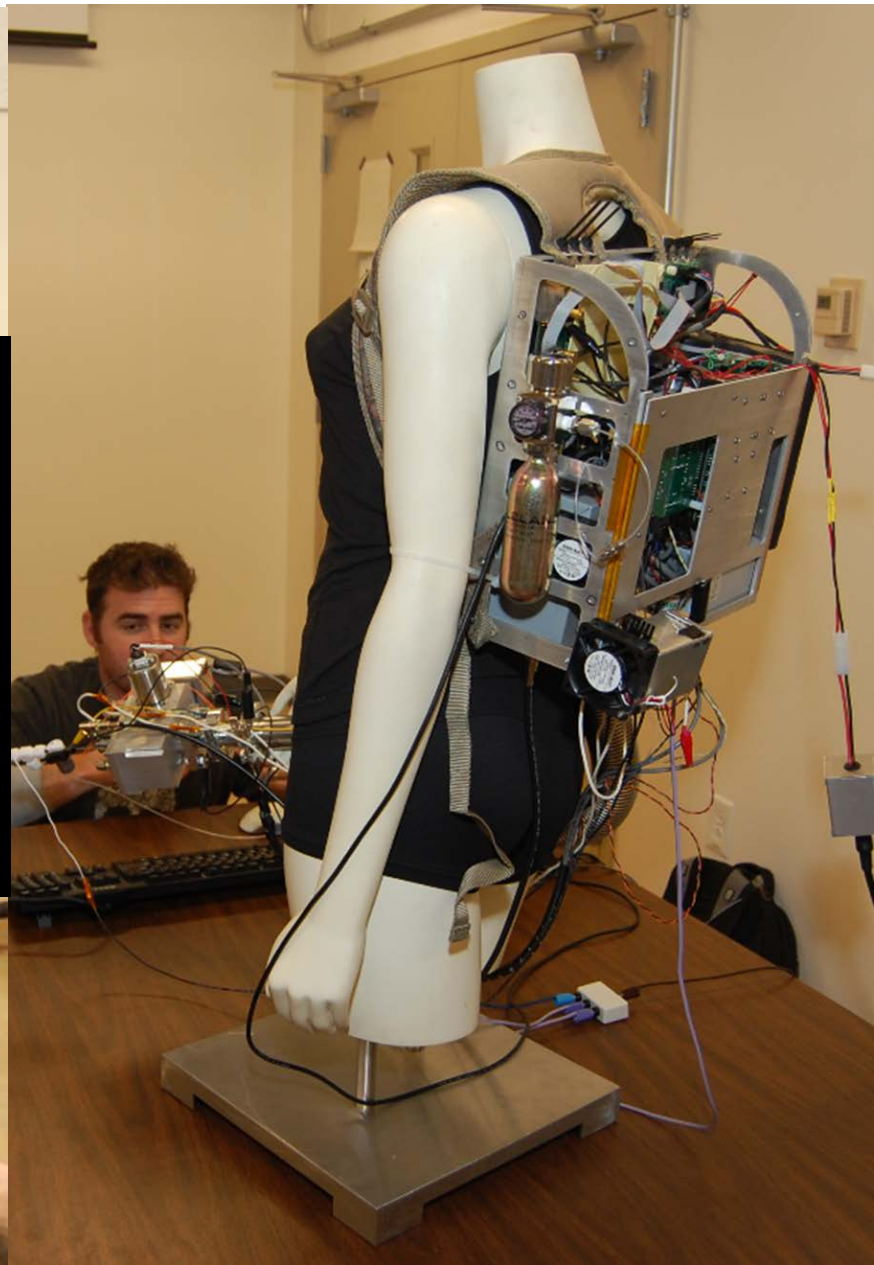




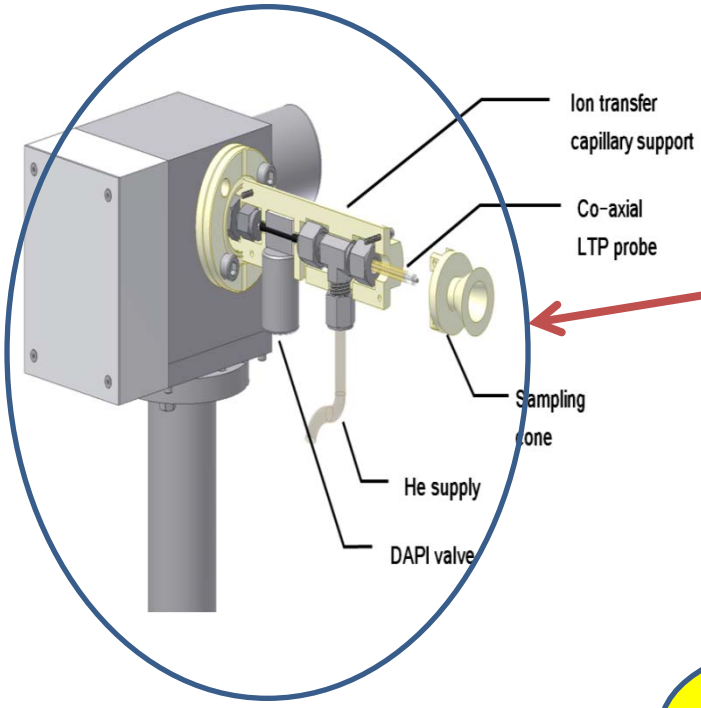
5x4x30 mm
6.5 kV @ 1MHz
> m/z 900

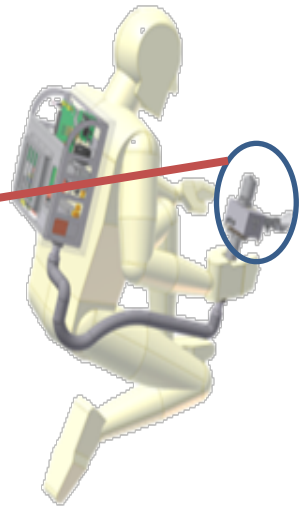
12,000 amu/s
1 – 2 amu FWhM
MS^n

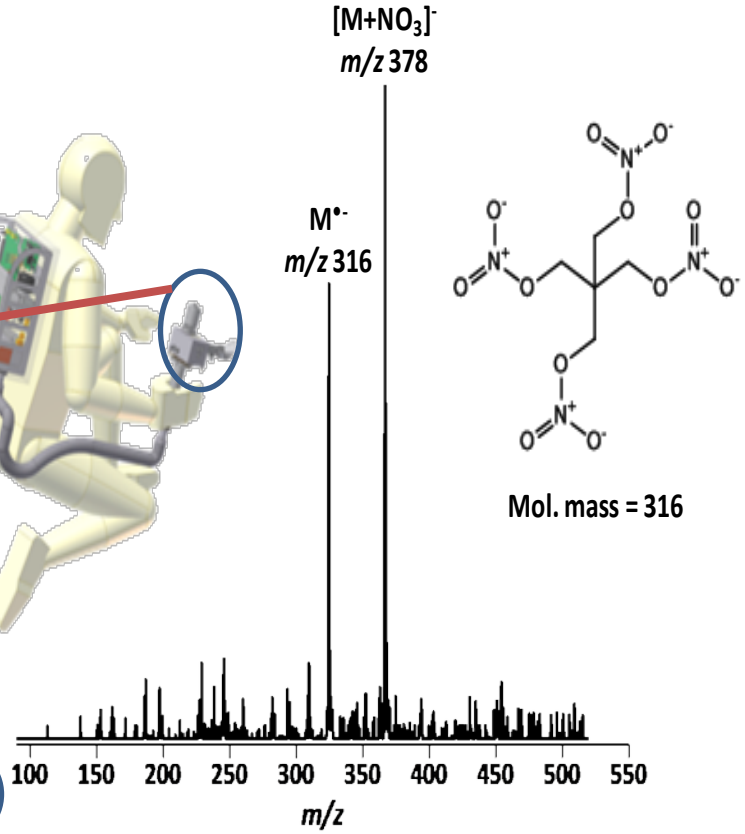
Paul Hendricks, et al. 2012s



Coaxial Low Temperature Plasma (LTP) on Backpack M







On Site

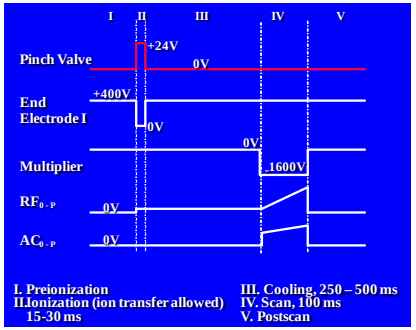
1 µg Pentaerythritol tetranitrate (PETN)

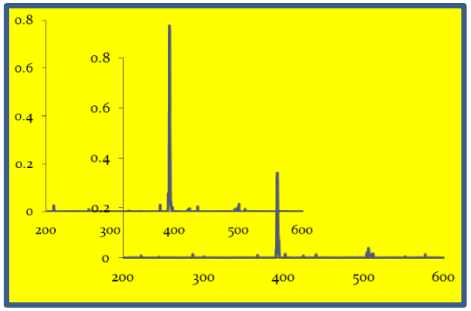
1 µg pentaethythritol tetranitrate (PETN) ionized from a surface (negative ions) using a low temperature plasma and analyzed using a backpack mass spectrometer

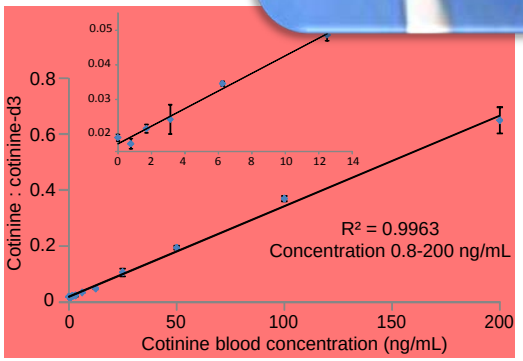
Paul Hendricks, *et al* *Analytical Chemistry*, in pr

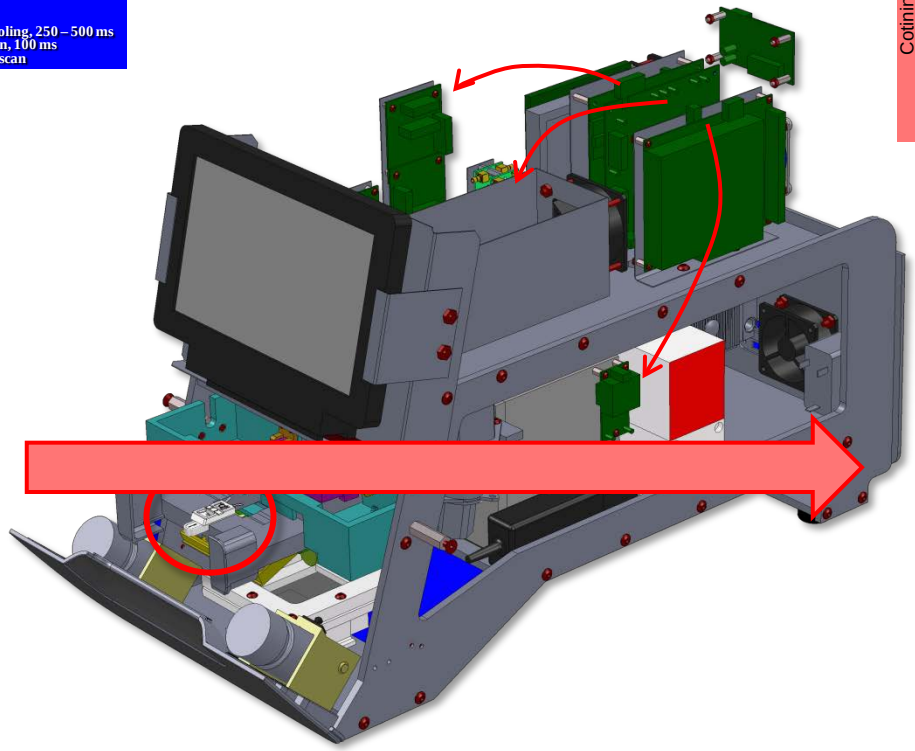
Mini 12

Expert system

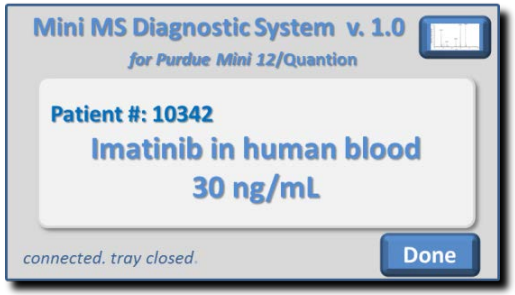






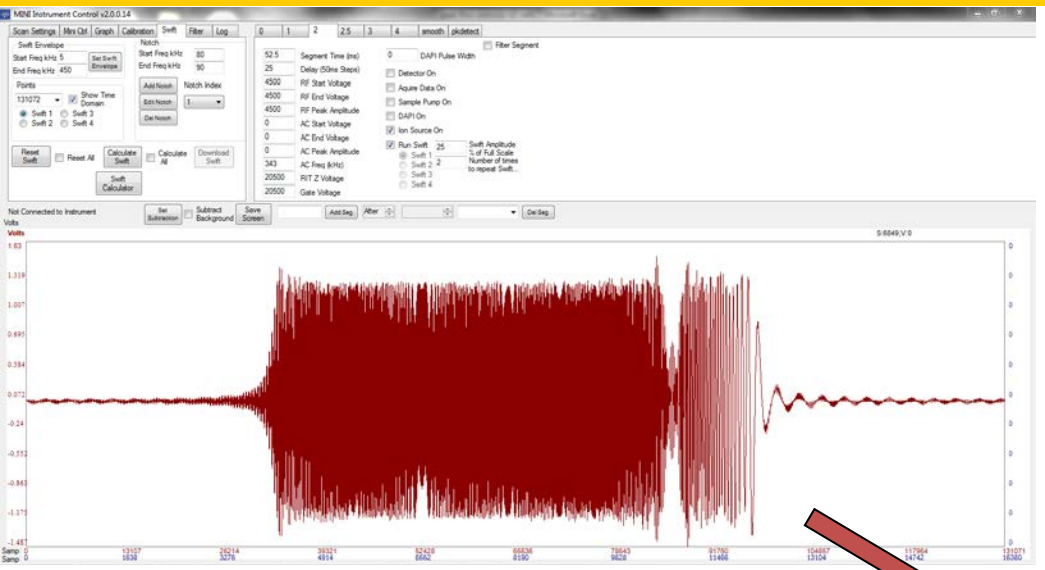


Novice GUI

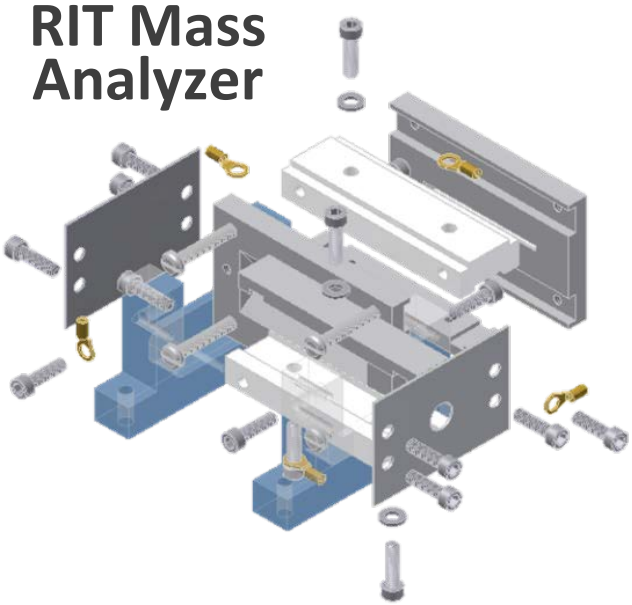


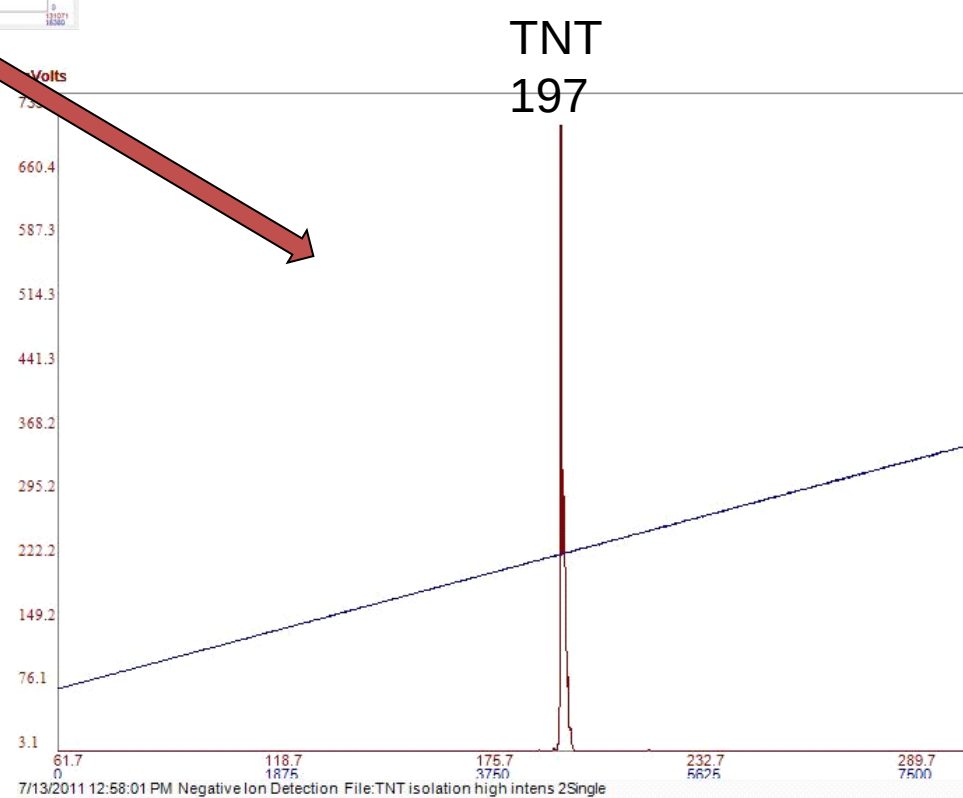
Linfan Li, *et al* *Analytical Chemistry*, in press

Analyte Detection/ID - SWIFT



- 80 - 90 kHz notch
- 2 V amplitude
- 2 SWIFT cycles



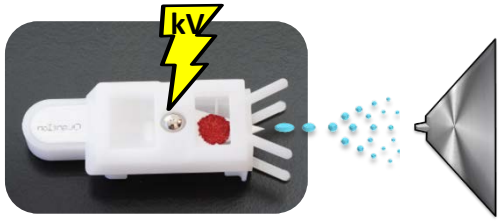


Paper Spray: Point-of-Care Analysis

MS/MS + Ambient + Mini MS

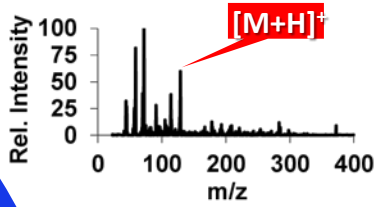
3. Apply Solution

4. Apply HV



2. Load Sample

5. Acquire Data

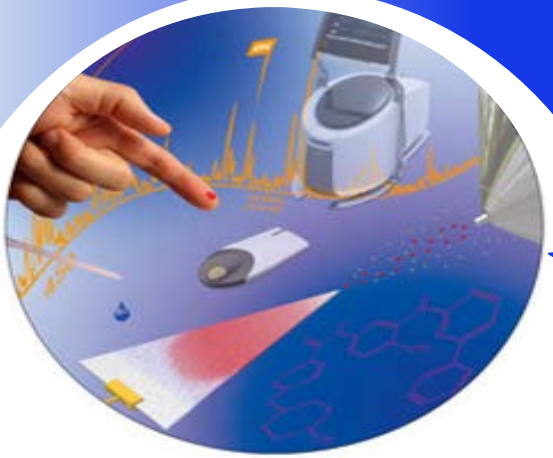


30 s

40 s

50 s

15 s

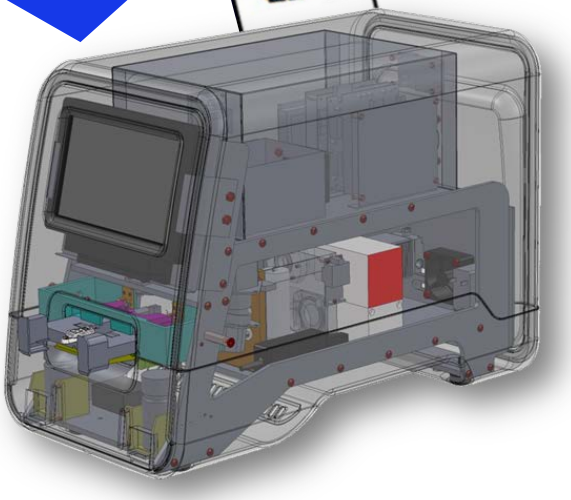


1. Prick Finger

0 s

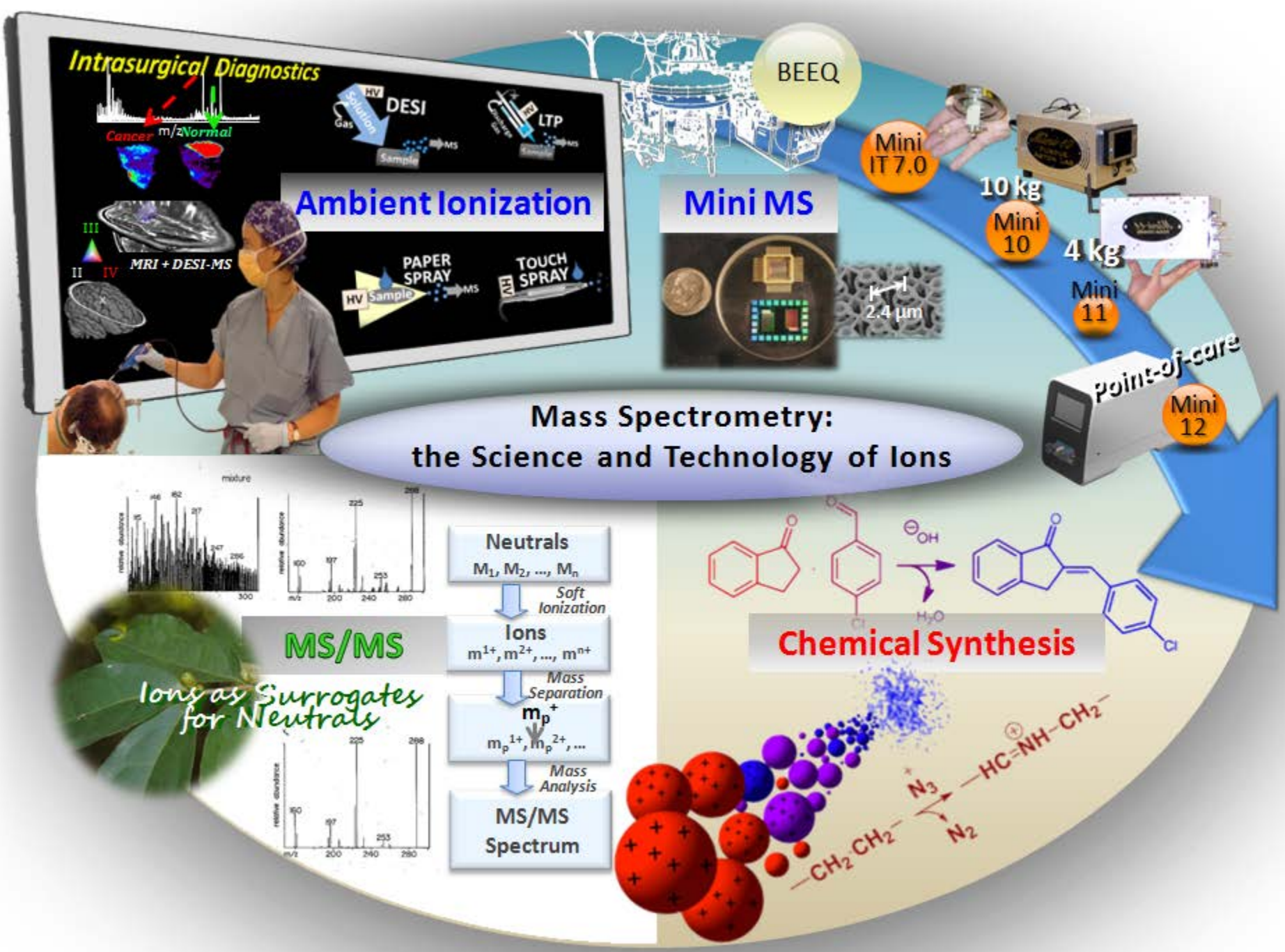
60 s

6. Report Results



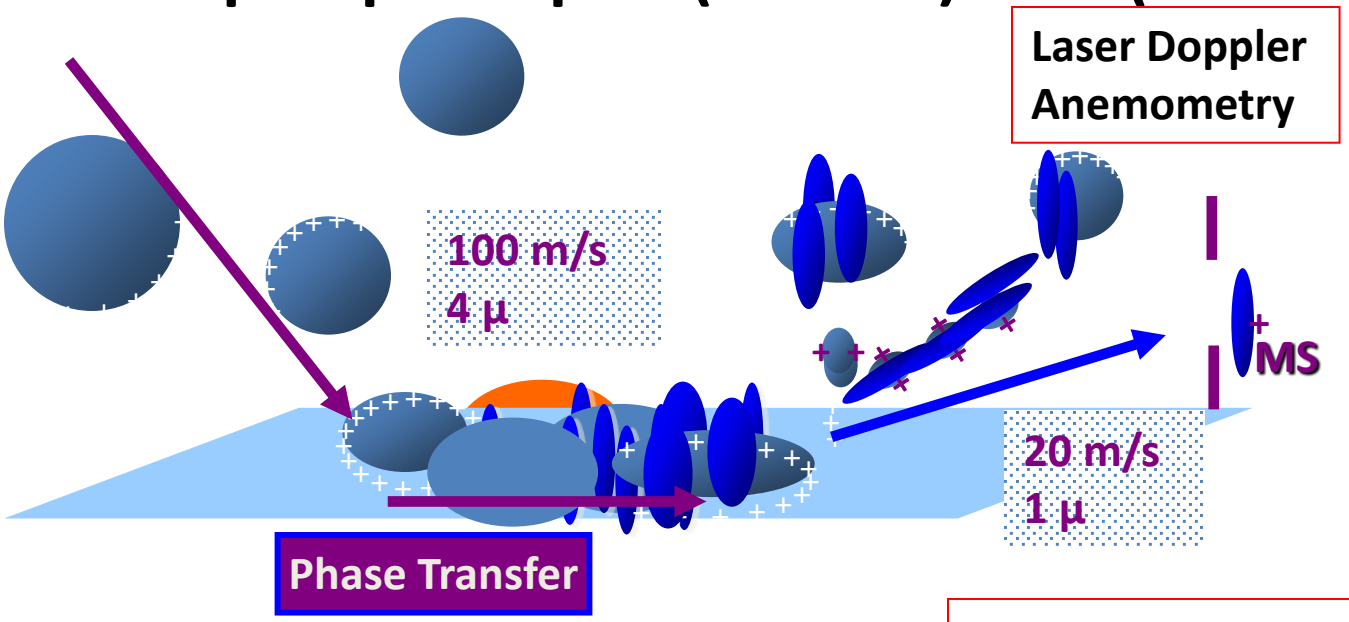
- One drop of blood
- 60 second analysis of biological samples
- Portable MS

He Wang, *et al. Angew. Chemie International Edition,* 2010, **49** 877;
Nicholas E. Manicke, *et al. Int. J. Mass Spectrom.,* 2011, **300,** 123


Intrasurgical Diagnostics
Cancer
m/z
Normal
MRI + DESI-MS
DESI
LTP
Ambient Ionization
PAPER SPRAY
TOUCH SPRAY
BEEQ
Mini MS
2.4 µm
Mini IT 7.0
10 kg
Mini 10
4 kg
Mini 11
Point-of-care
Mini 12
Mass Spectrometry:
the Science and Technology of Ions
Neutrals
$M_1, M_2, ..., M_n$
Soft Ionization
Ions
$m^{1+}, m^{2+}, ..., m^{n+}$
Mass Separation
m_p^+
$m_p^{1+}, m_p^{2+}, ...$
Mass Analysis
MS/MS Spectrum
MS/MS
Ions as Surrogates for Neutrals
Chemical Synthesis

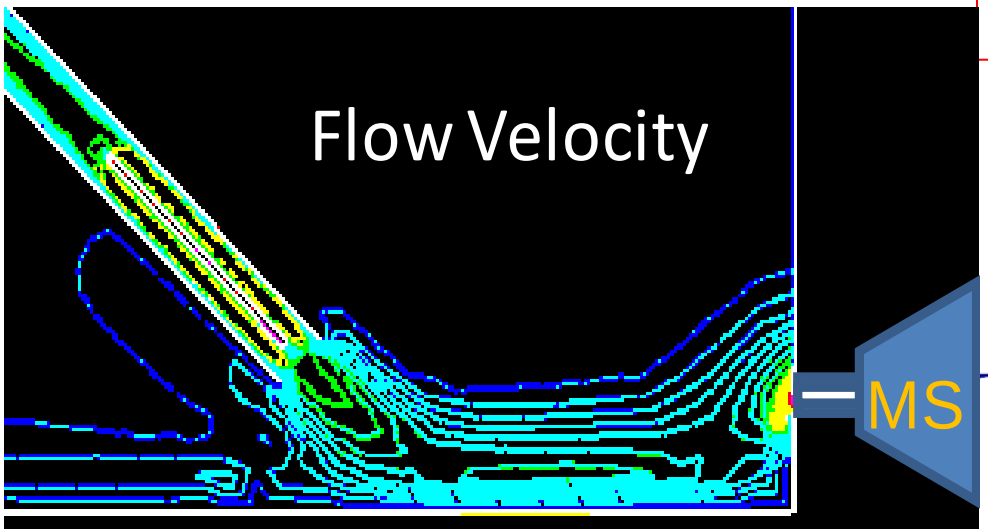
DESI Mechanism

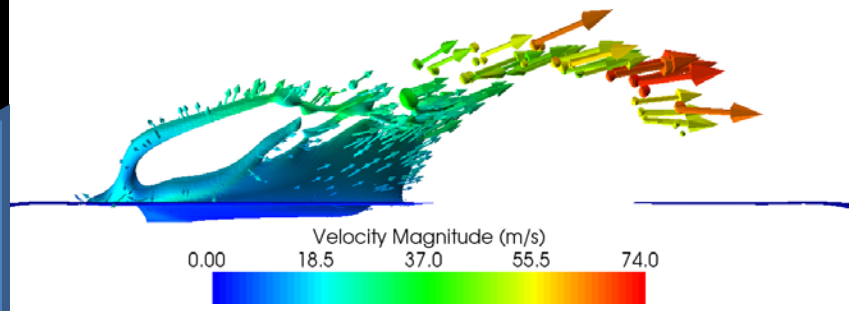
Droplet pick-up: A (surface) → A (solution) → A^+ (gas)



Venter, Sjoka, Cooks, Anal. Chem. 2007
Costa & Cooks, 2008

Simulations w/o Electric fields





Importance of Bursting Bubbles

Chemical Separation upon Bubble Bursting

DOM from sea surface moves into atmosphere via bubble bursting. This involves adsorptive bubble separation leads to preferential concentration of surface active compounds in the bubble jet droplets. ca. 10^{19} bubbles per second – large quantities of functionalized hydrocarbons go into air.

Phil. Schmitt-Kopplin et al. Biogeosciences Discuss., 8, 1–27, 2011

www.biogeosciences-discuss.net/8/1/2011/

www.biogeosciences.net/10/1583/2013/

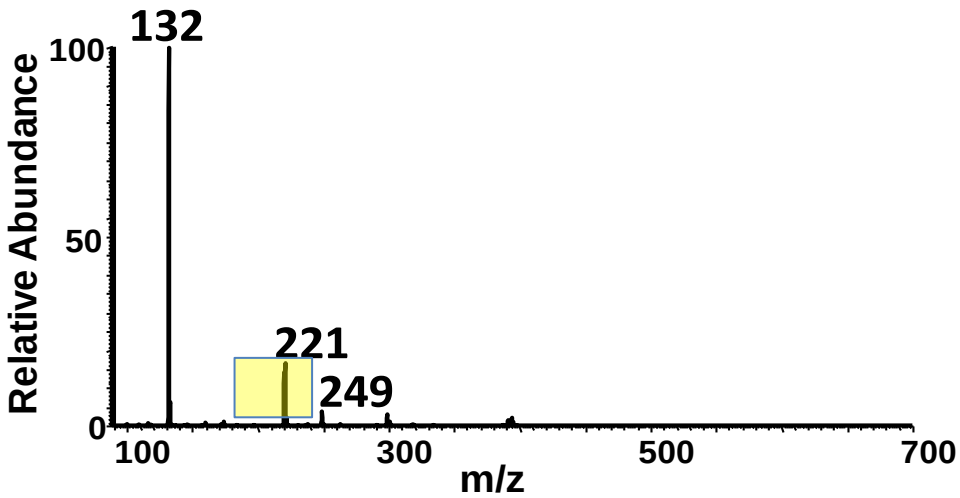
This mechanism might also lead to prebiotic cells -- Barny Ellison

Christopher M. Dobson, G. Barney Ellison, Adrian F. Tuck & Veronica Vaida, PNAS, 97, (2000) 11864 –11868

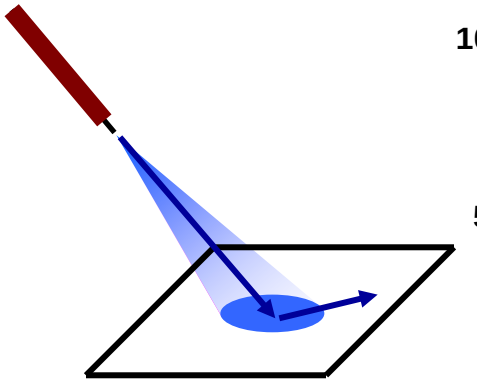
"Atmospheric aerosols as prebiotic chemical reactors"

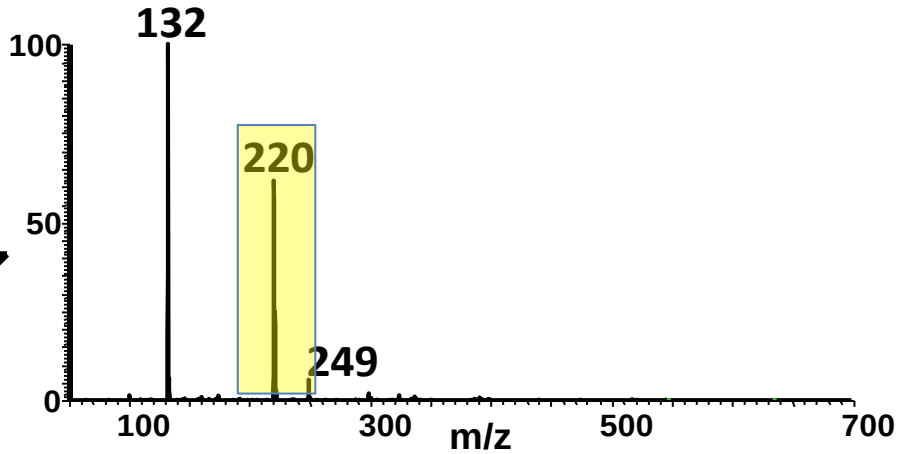
MS Synthesis: Nanospray Girard T/Benzaldehyde

a) 1 h bulk solution-phase (Benzaldehyde + Girard T in ACN 1000 ppm)



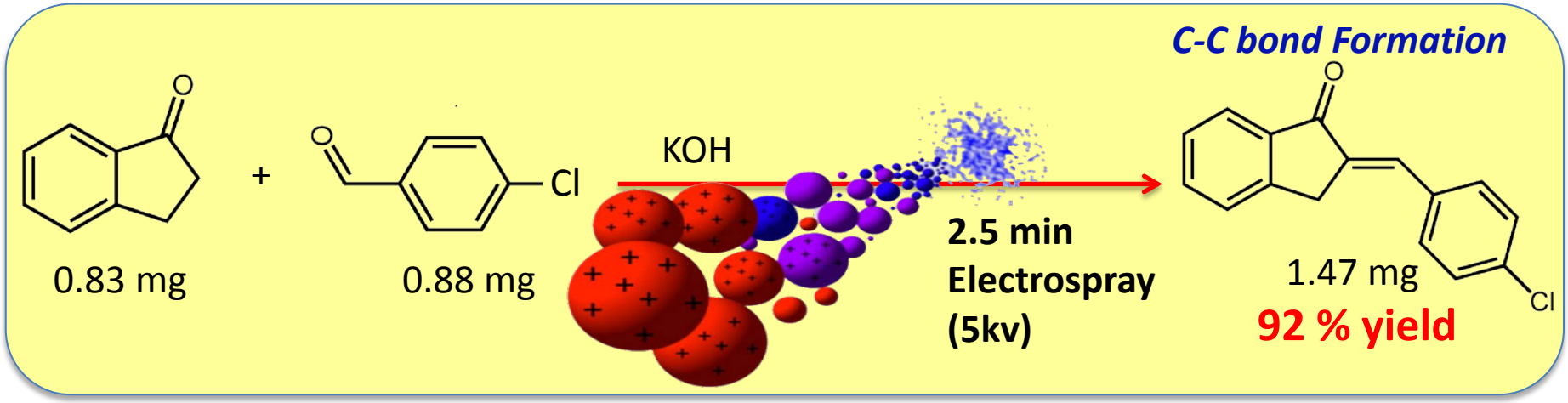
b) <1 min Reactive DESI (5 µL/min 1000 ppm benzaldehyde)

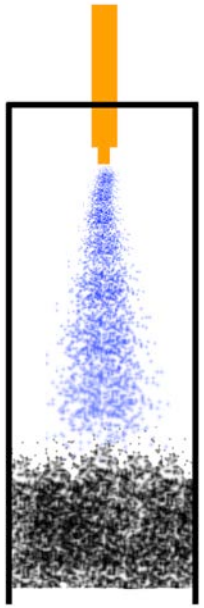


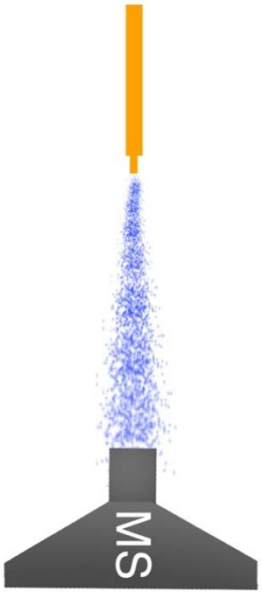


Abraham Badu-Tawiah;
Thomas Mueller

MS Synthesis: Claisen-Schmidt Condensation

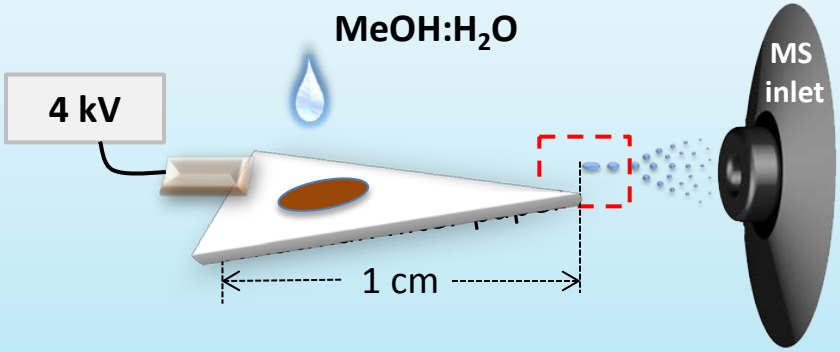


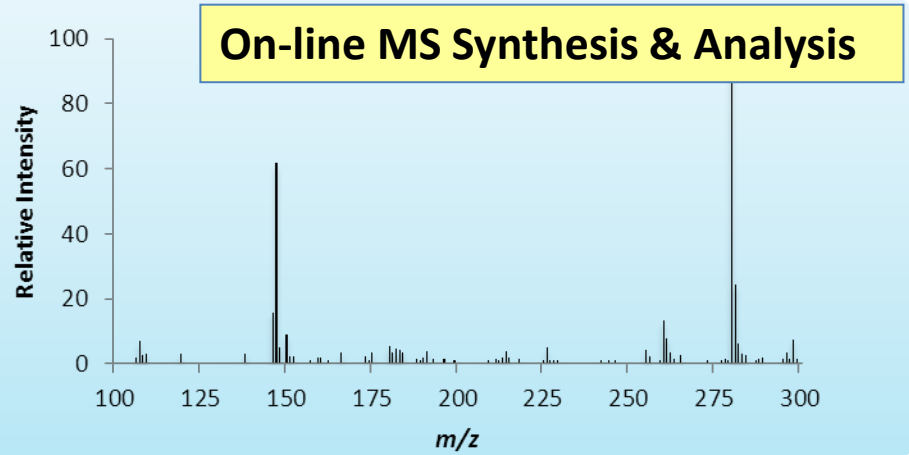


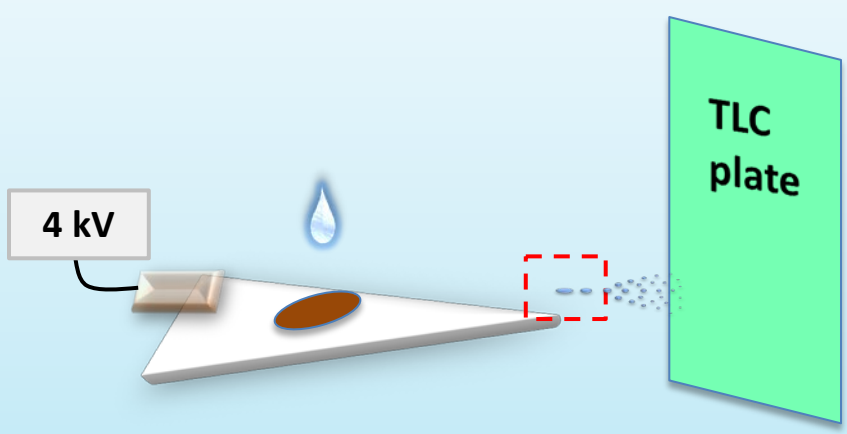


Thomas Müller, Abraham Badu-Tawiah, R. G. Cooks, *Angew. Chem*. (2012)

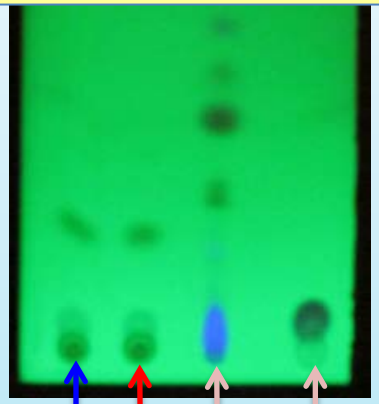
Spray Synthesis: Claisen - Schmidt Condensation







On-line MS Synthesis & Off-line TLC Analysis



Traditional bulk-phase reaction: 1 hr

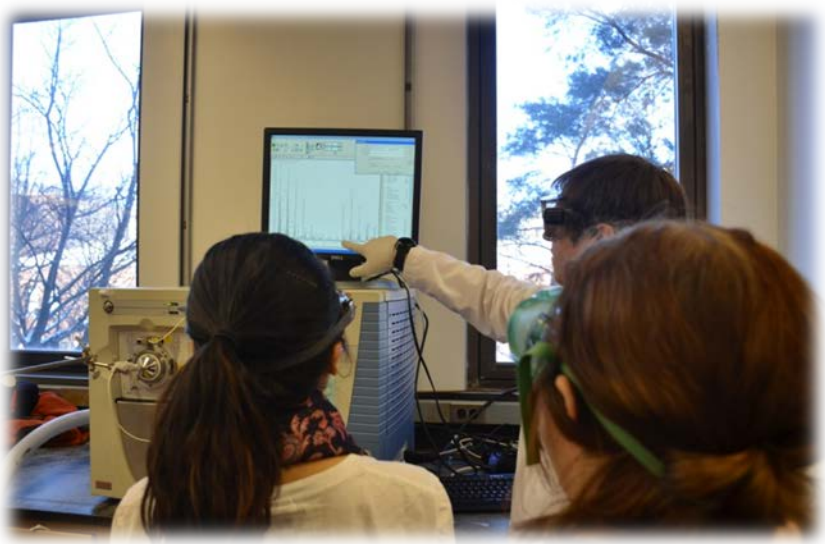
Spray synthesis "spotting time": 30 sec

Benzaldehyde (starting material)

Indanone (starting material)

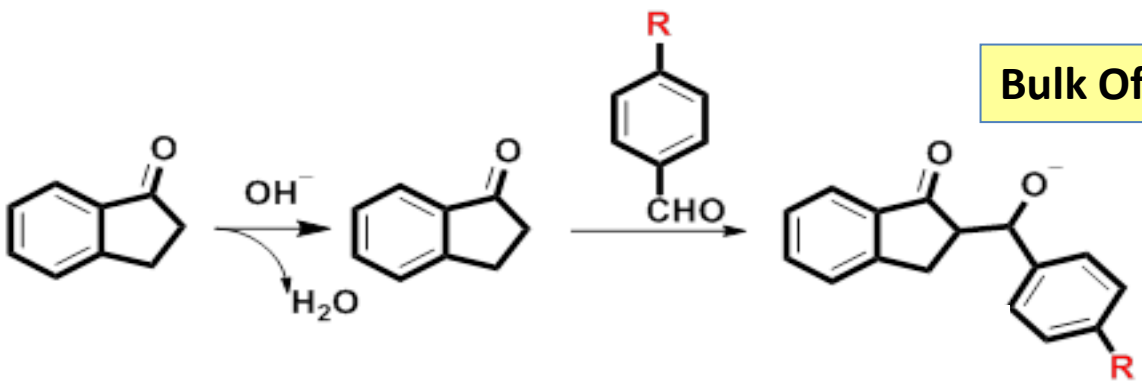
Ryan Bain, Chris Pulliam

MS Synthesis: Undergrad Organic Lab



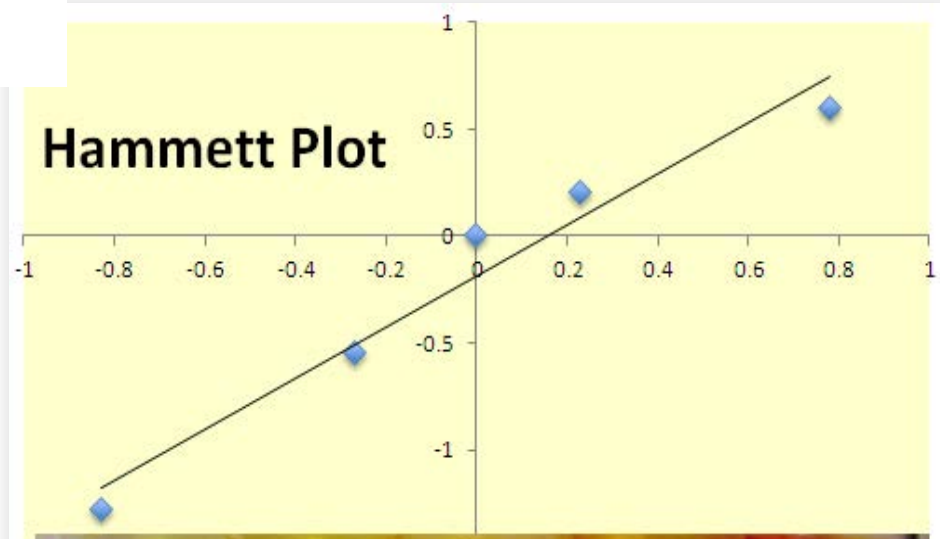
Ryan Bain, Chris Pulliam

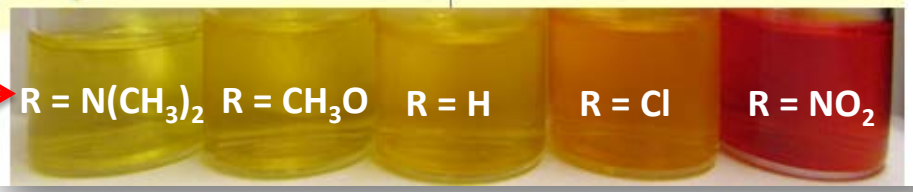
Rapid Survey of Substituent Effects on Claisen-Schmidt Reaction



Bulk Off-line Synthesis then MS Analysis

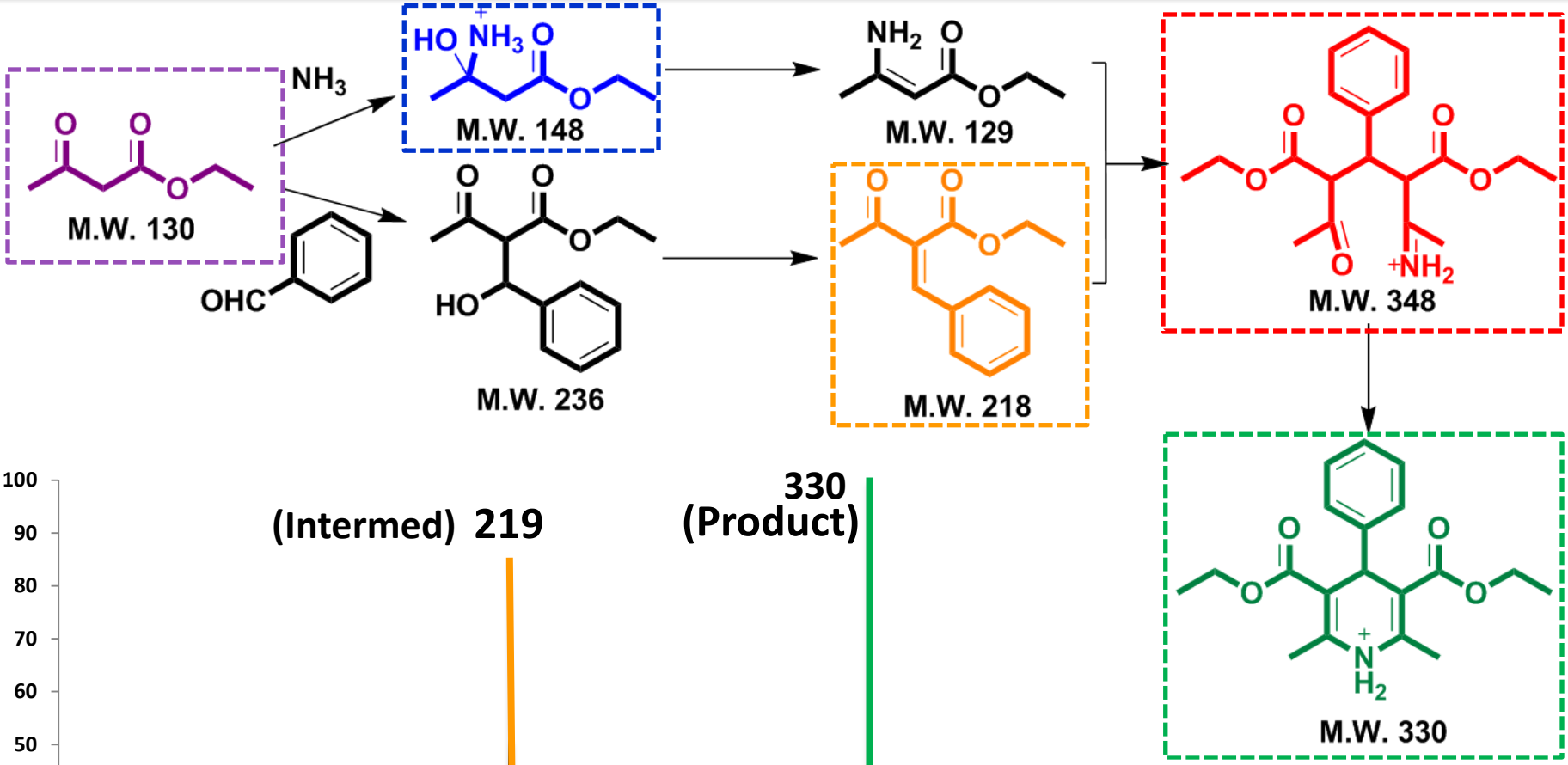
- Paper spray reaction : **instantaneous**
- Plot MS measure product/reactant peak intensity vs Hammett sigma to study **substituent effects**
- Suitable for **sophomore organic lab**

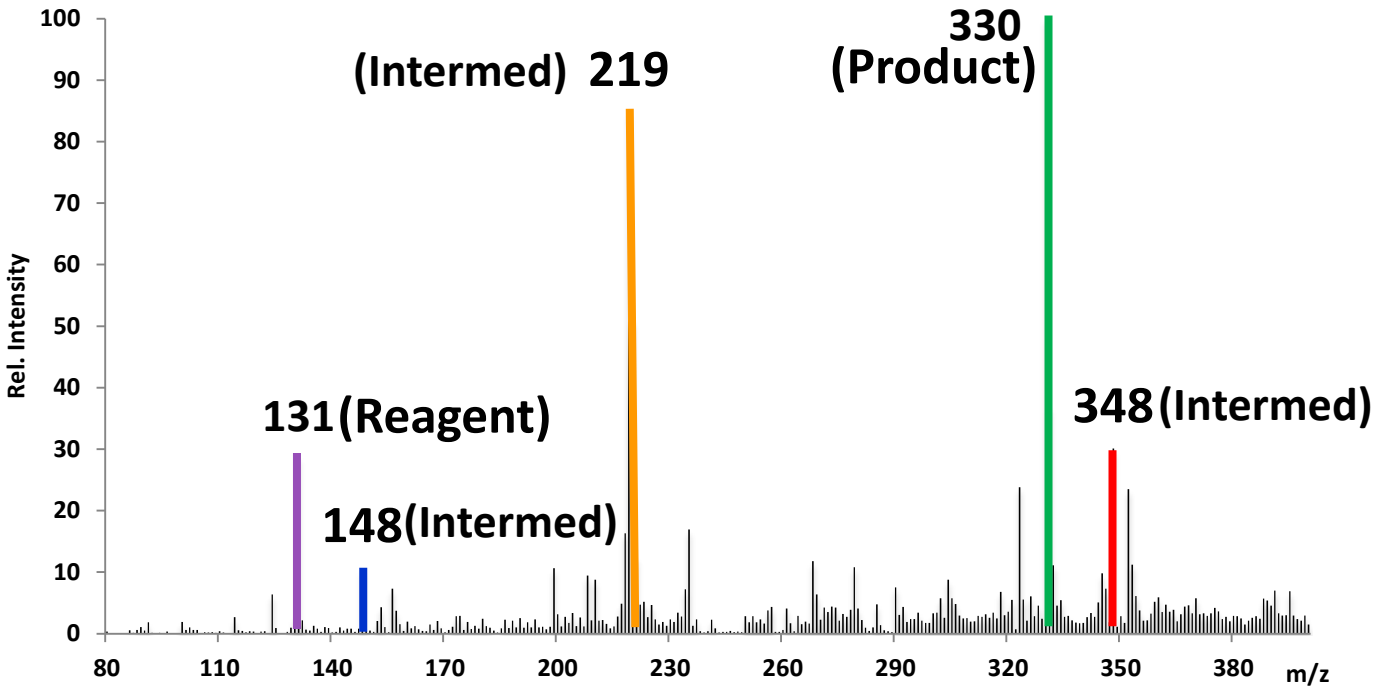


Rxn Mix. → 

Ryan Bain, Chris Pulliam

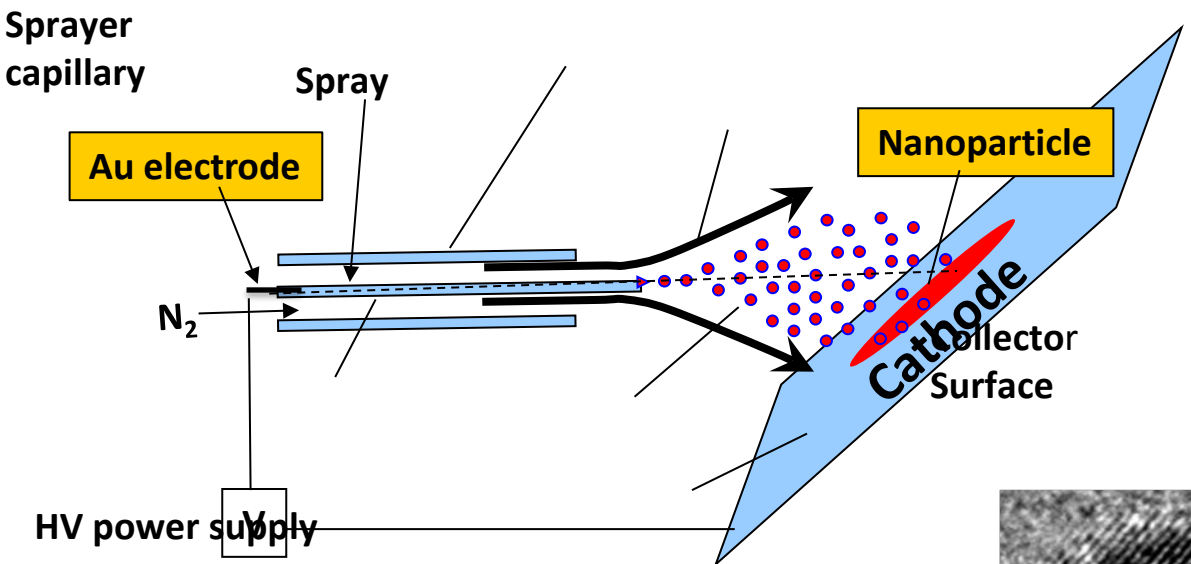
Intermediates in MS Synthesis: Hantzsch Reaction

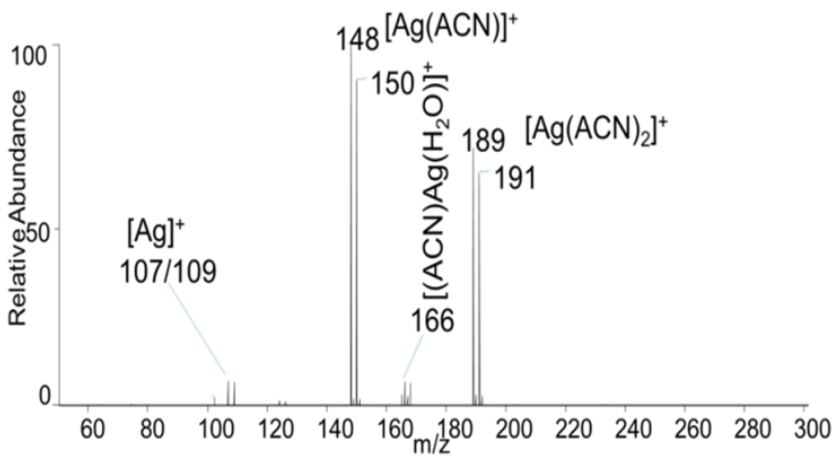


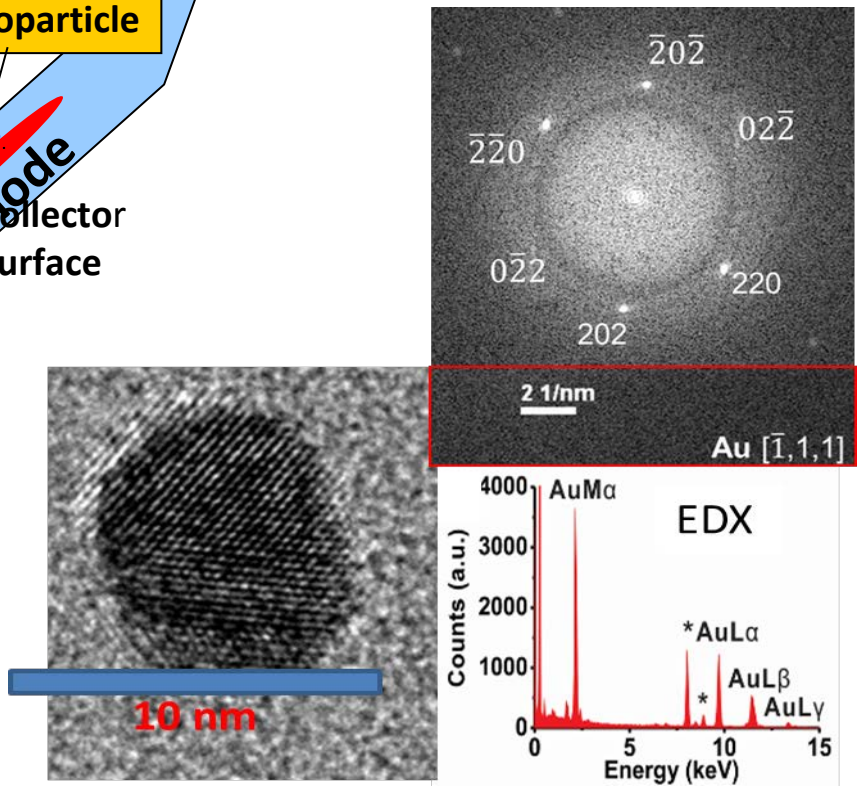


Ryan Bain, Chris Pulliam

Electrocorrosion/electrospray NP Synthesis

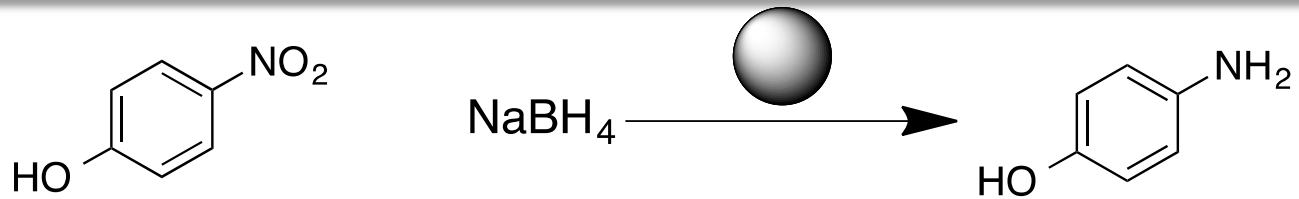




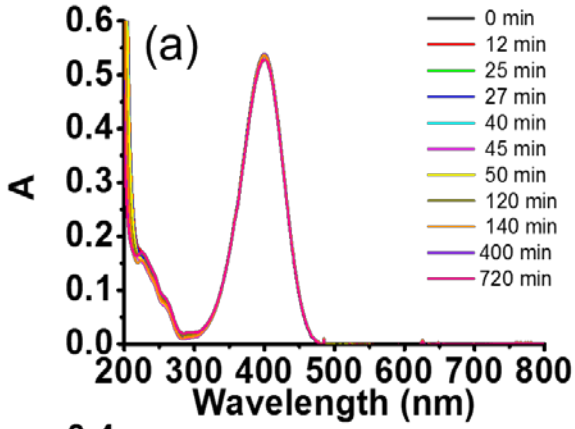


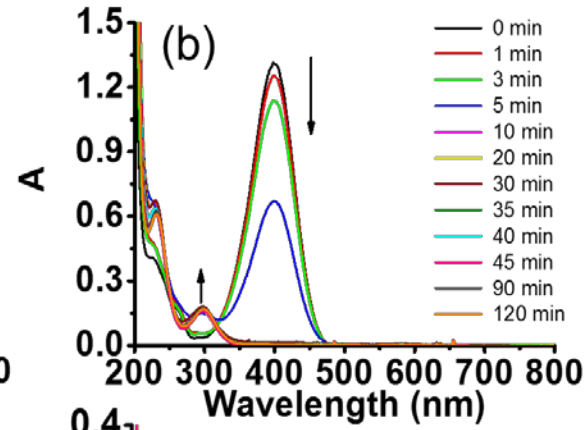
Anyin Li, *et al, Angew. Chem.* in press

Offline & online *p*-Nitrophenol Catalysis by NP



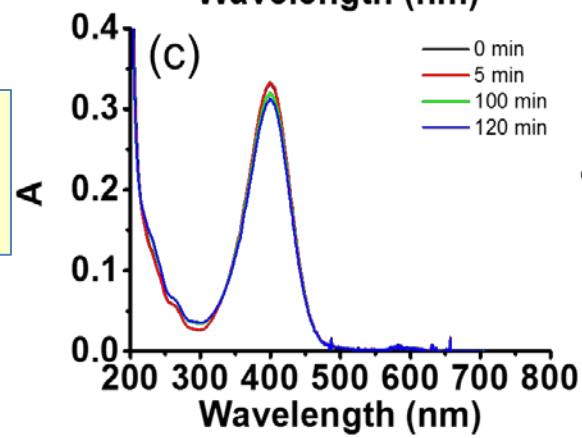
Without AuNP

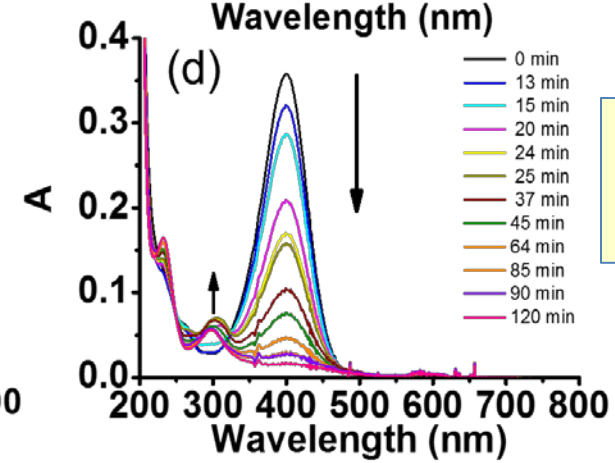




AuNP prep off-line

Control: protic solvent into rxn mixture





Au^+ ion in charged droplets (10 nA) on surface rxn mixture

Nanoparticles prepared offline or online catalyze p-nitrophenol reduction by sodium borohydride uv-vis spectra of 4-nitrophenol reaction mixture, peak at 400 nm (n→π* transition of p-nitrophenol anion)

Anyin Li, *et al, Angew. Chem.* in press

Catalytic Activity: Off-line & On-line NP vs. Lit

	Catalyst	Capping agent	size/nm	Au conc (mg/mL)	4-NO_2 phenol (mM)	$NaBH_4$ (mM)	Rate Const k (s^{-1})	k/Au conc (mL· $s^{-1}mg^{-1}$)	Ref
Lit.	AuNP@Fe_3O_4	Oleylamine	~5	1.73E-01	0.18	7.27	0.0105	0.061	2011, Doong
	AuNP	Citrate	~10	5.25E-01	0.22	10.99	0.00069	0.001	2011, Seoudi
	AuNP	CTAB	~9	5.25E-01	0.22	10.99	0.00193	0.004	
	Au nano cage	PVP	50	2.35E-03	0.0014	0.42	0.0472	20.1	2010, Xia
	Au nanobox	PVP	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
	Hollow nanobox	PVP							
	Au@*hm*-ZrO_2	HS-C11 acid							2010, Zhao
AuNP off-line	Catalyst	Capping Agent						conc $^{-1}mg^{-1}$)	
	AuNP	CTAB							This
Deposit in situ	Catalyst	Capping agent	size/nm	Au delivery (mg/mL· s)	4-NO_2 phenol (mM)	$NaBH_4$ (mM)	App Rate constant k' (s^{-2})	2k'/Au delivery rate (mL· $s^{-1}mg^{-1}$)	
	Au^+	CTAB	N.A.	1.22E-08	0.024	3.79	8.00E-06	1309	This
	Au^+	None	N.A.	1.11E-08	0.024	3.60	8.00E-07	143.8	This

Interim conclusion:

Powerful, simple method

Applic. to nano/energy projects

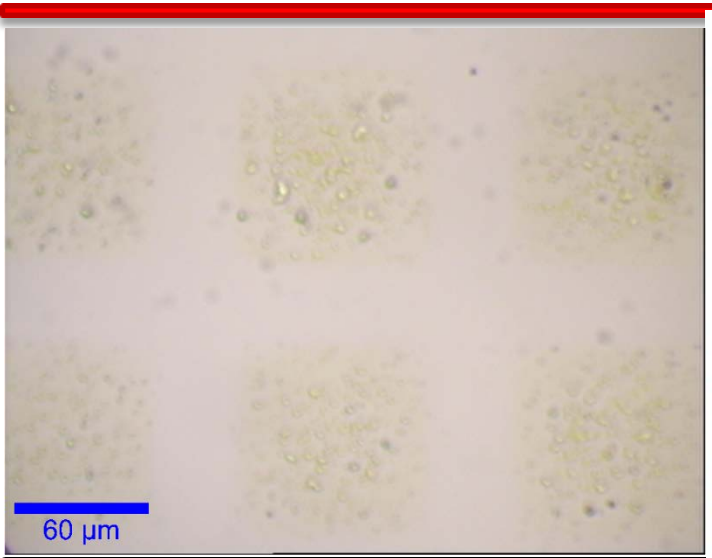
Many other materials by adding ligands

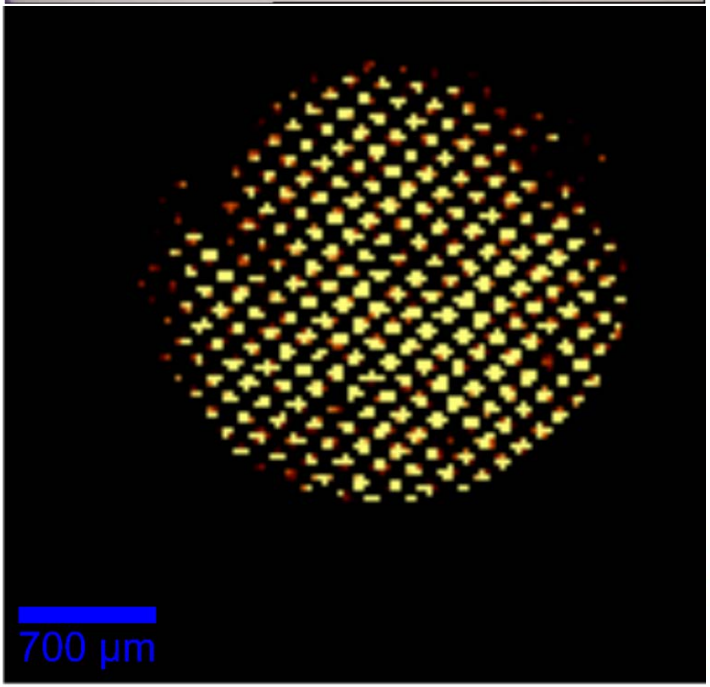
Catalytic activity

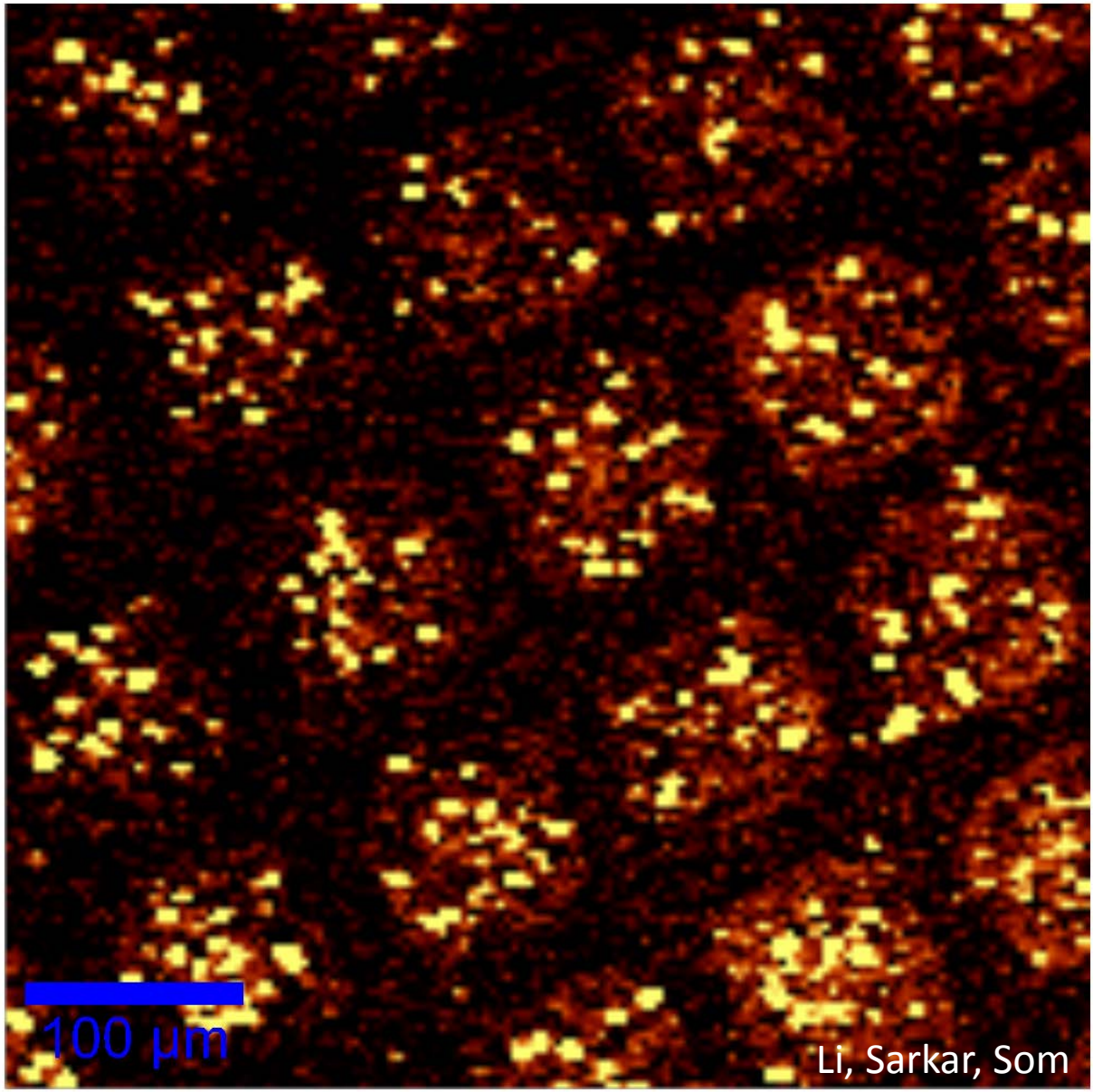
SERS activity

Anyin Li, *et al, Angew. Chem.* in press

SERS active patterns

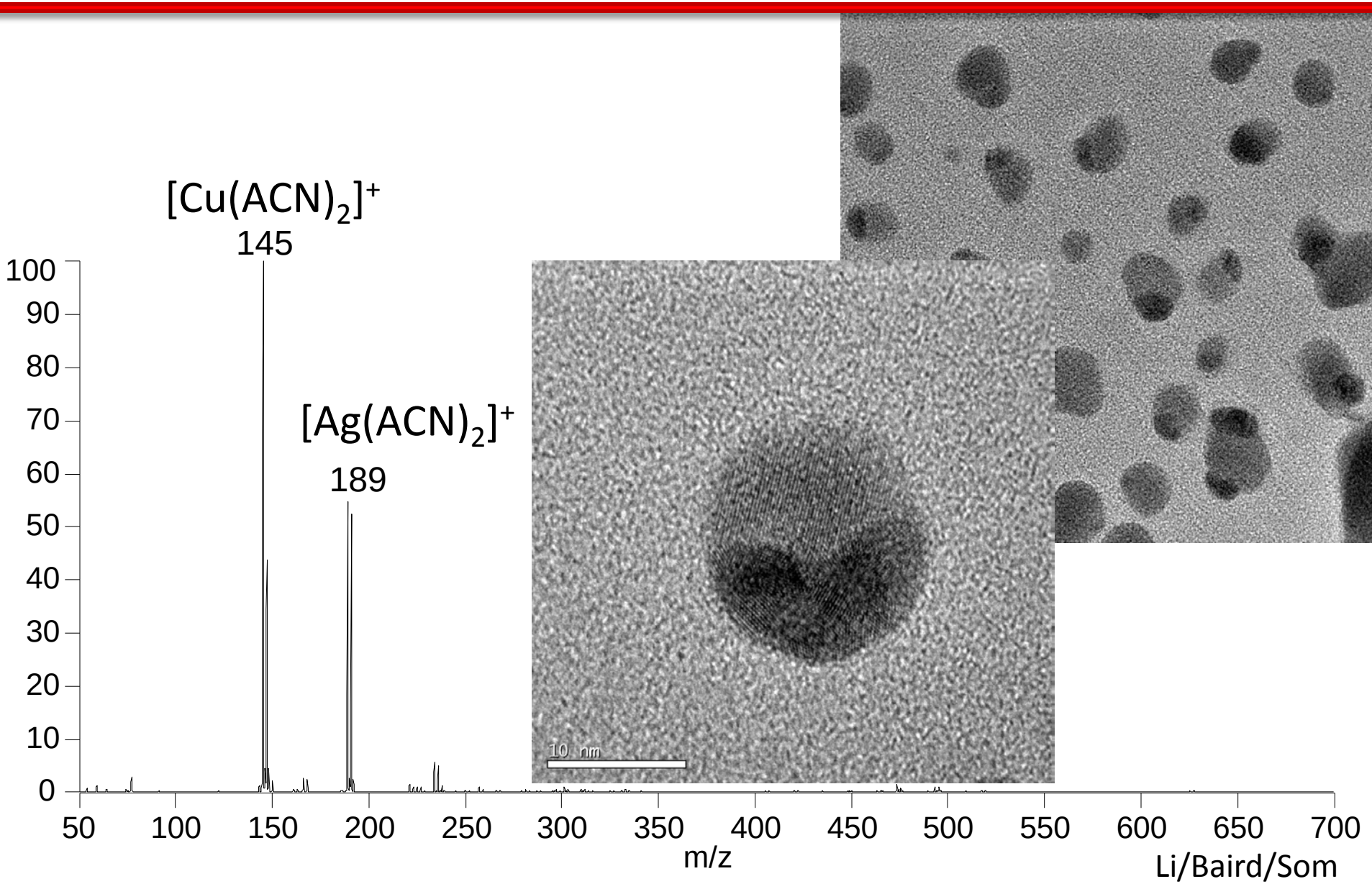






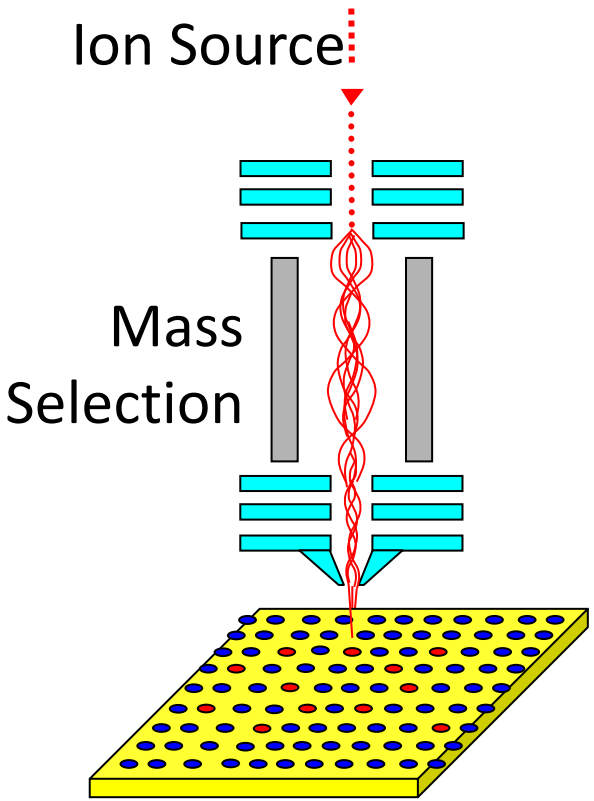
Li, Sarkar, Som

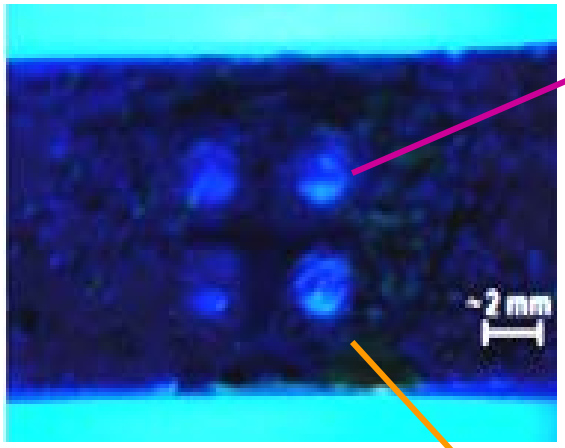
Atomic mixing toward Janus/alloy particles

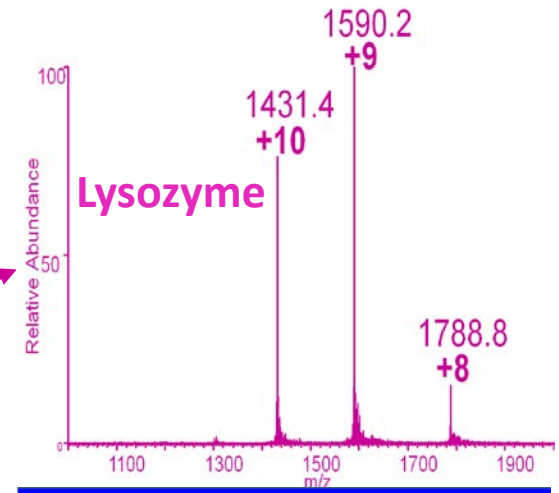


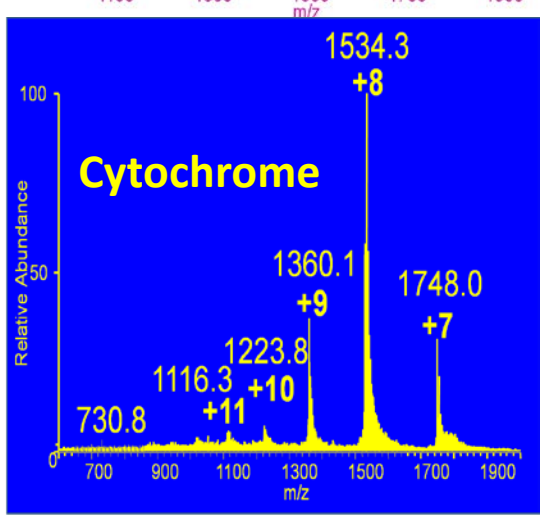
Protein Soft-Landing

Isolation from mixture and subsequent collection of intact proteins



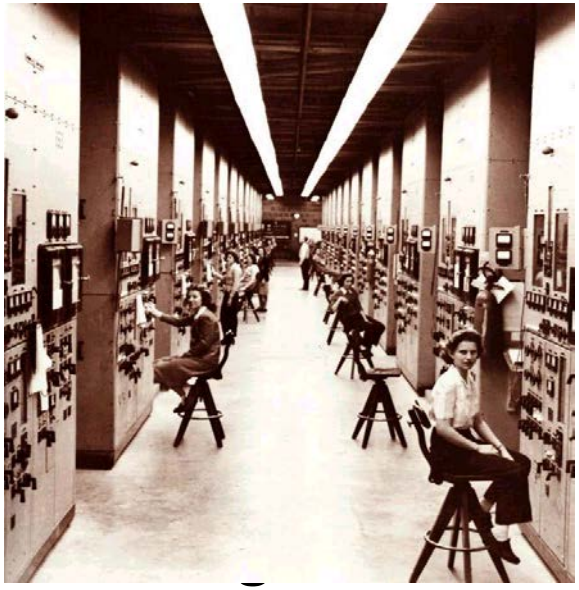


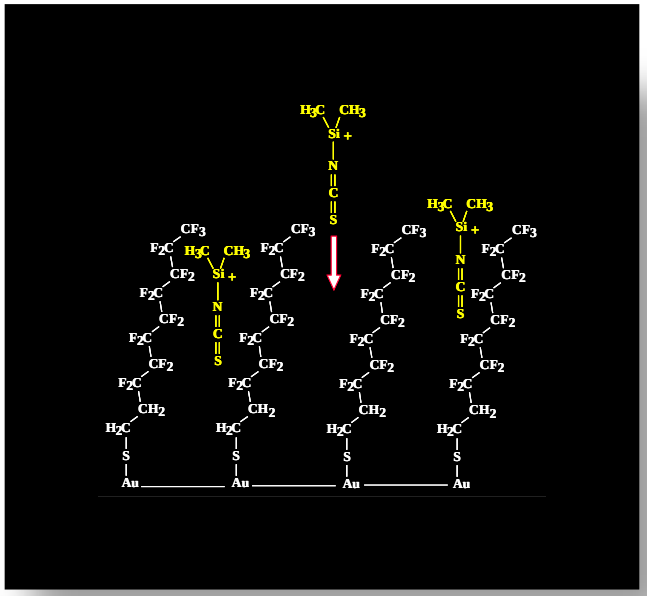


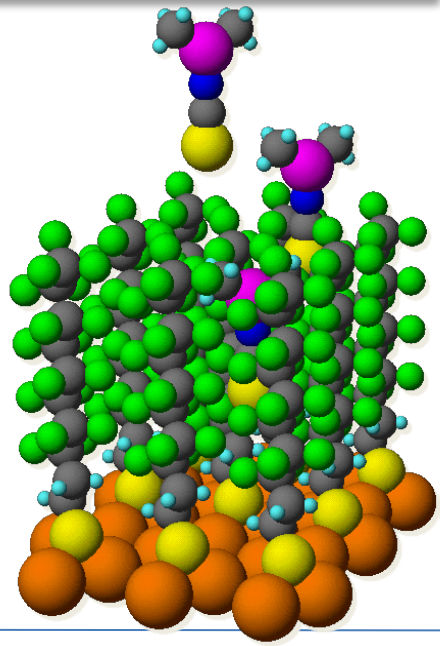


Z. Ouyang, *et al. Science* 301, 1351 (2003)

Synthesis by Mass Spectrometry

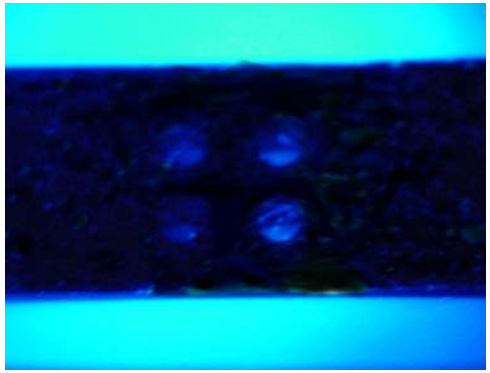




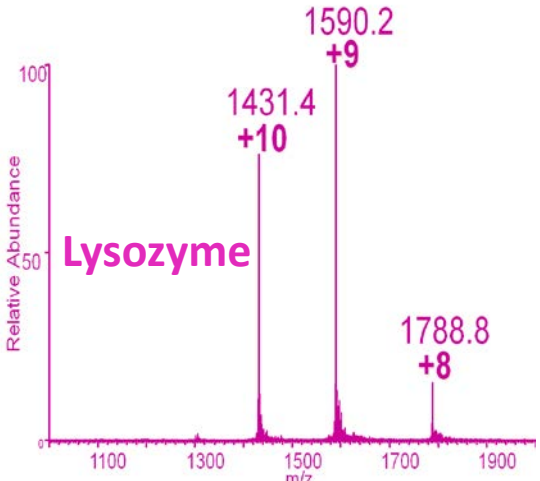


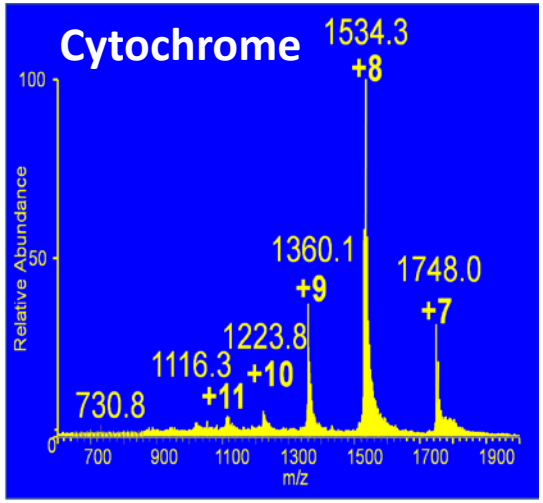
Oak Ridge Ion Deposition

Soft Landing of Protein Ions



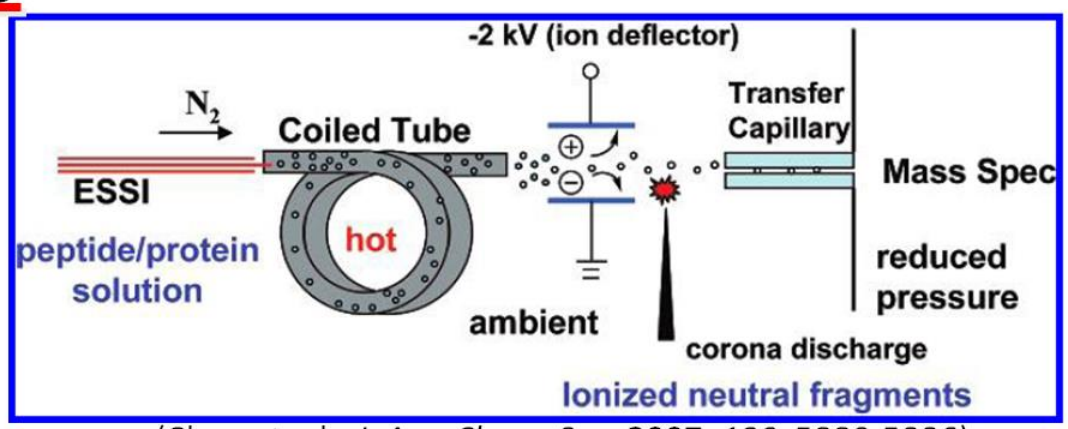
Protein arrays – µg/hour



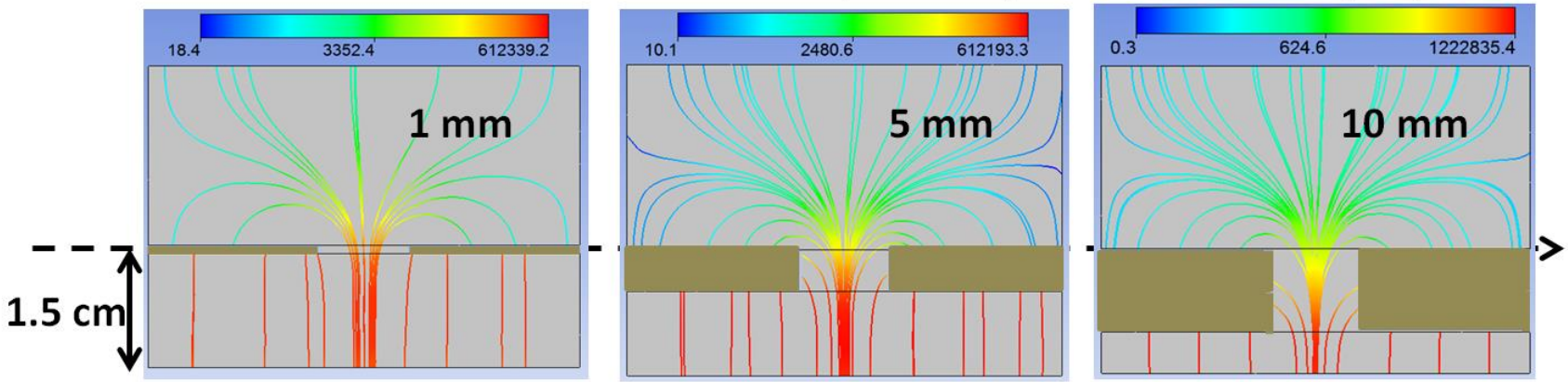


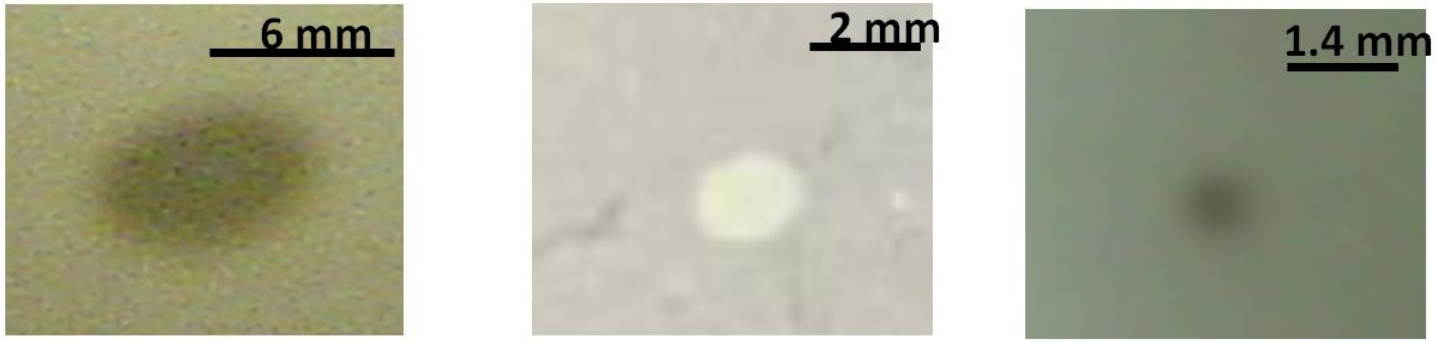
Ambient Ion Soft Landing

Hao Chen



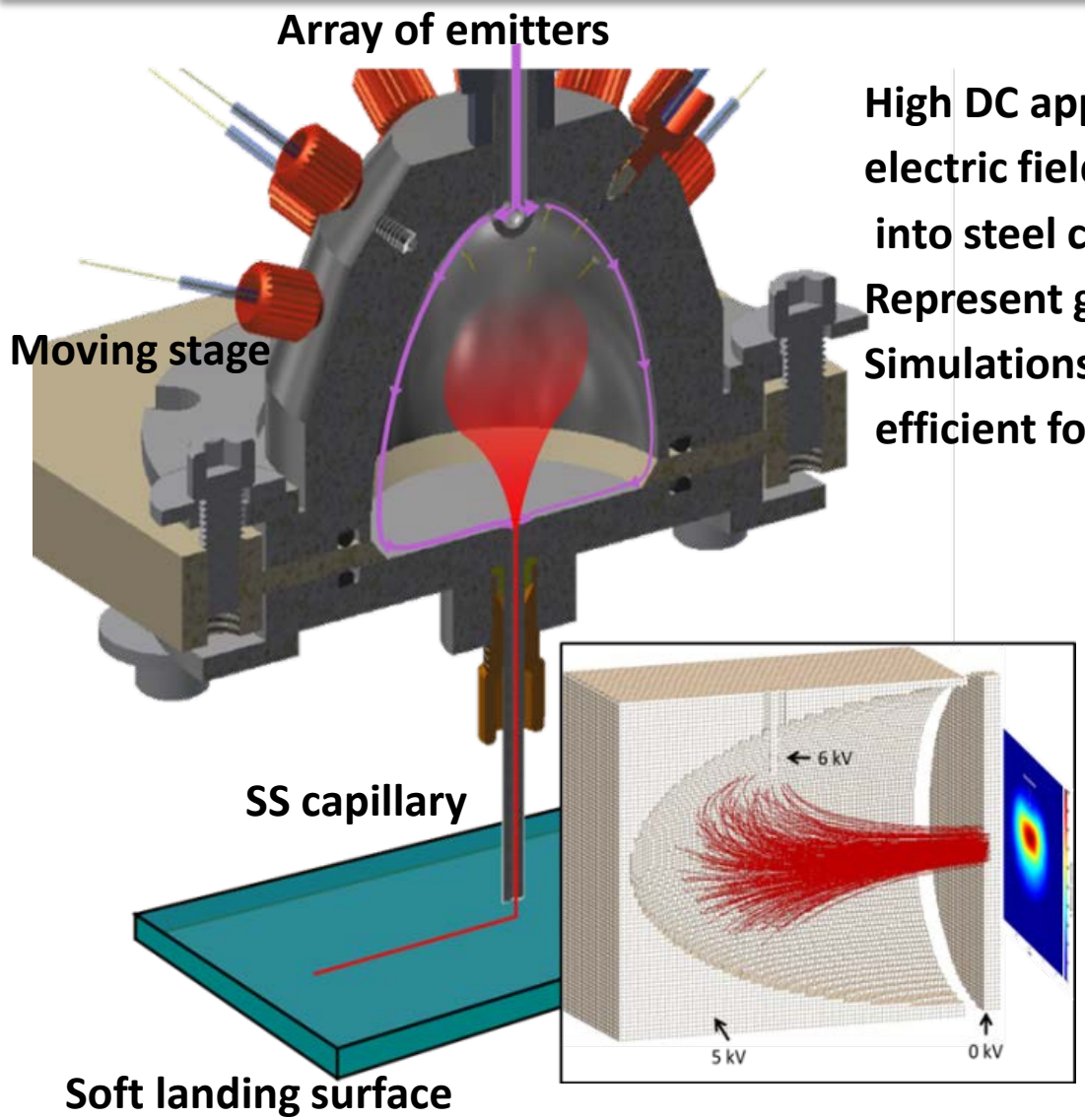
(Chen et. al., *J. Am. Chem. Soc.* **2007**, *129*, 5880-5886)





Abraham Badu-Tawiah

Array of Electrospray Emitters for Ambient Ion Soft Landing



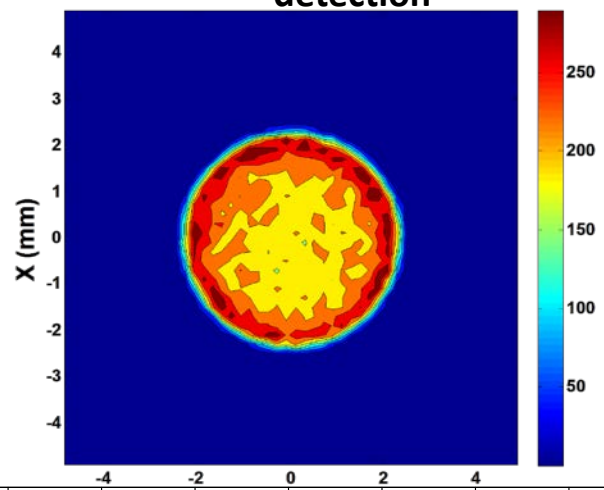
High DC applied to focusing electrode, creating an electric field that with pneumatics, focuses the ions into steel capillary. Purple lines and red area Represent gas flow and focused ion cloud. Simulations of ion trajectories indicate a highly efficient focusing process.

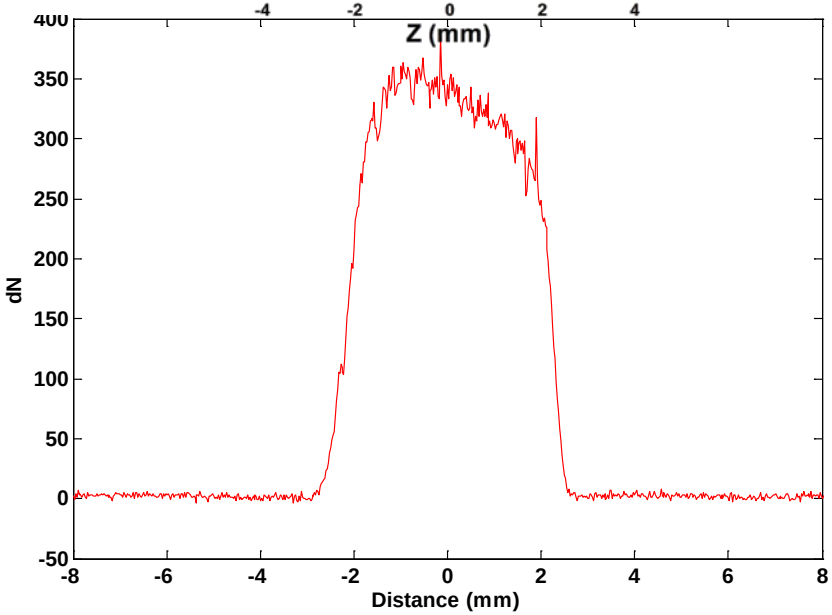
Experiments confirm high deposition efficiency {ca. 75%}
(inset) Simulation of ions/charged droplets motion

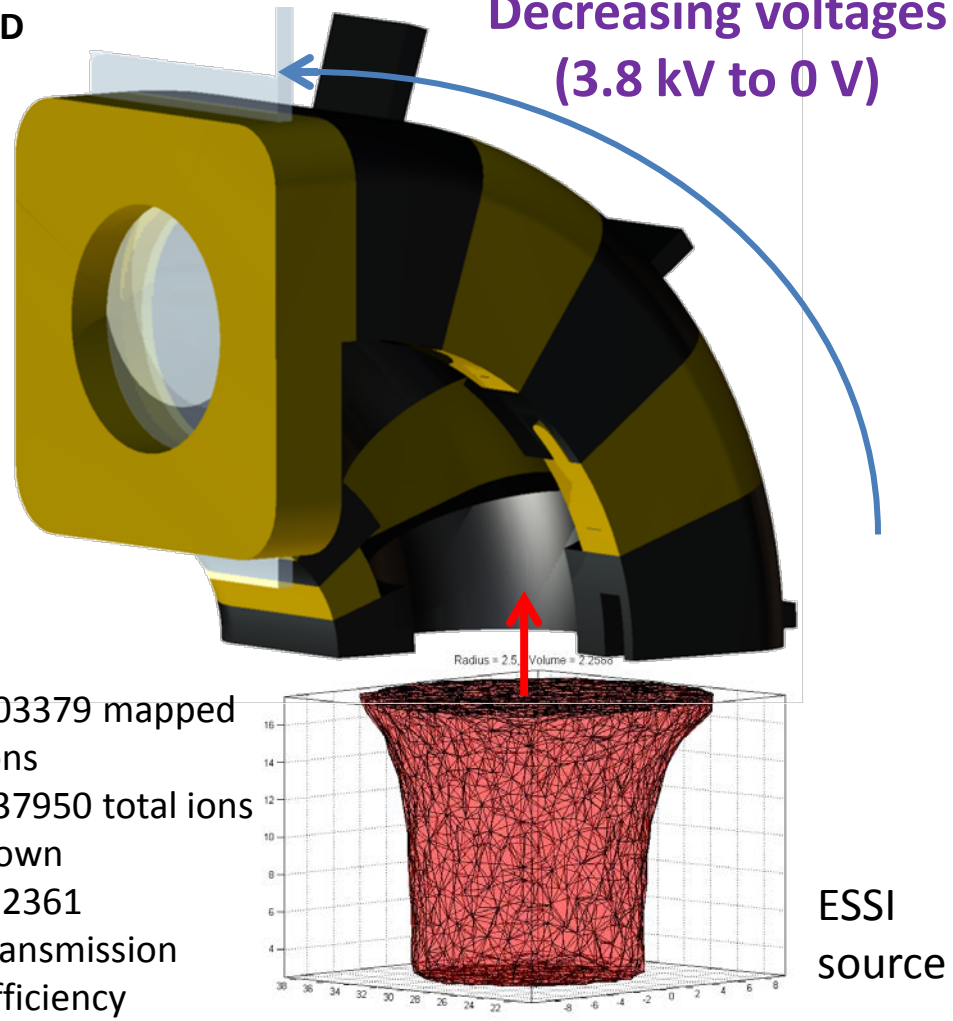
Zane Baird

MS & Ion Optics in Air – Simulation & Expt

Comparison of simulated deposition spot(top, SIMION) and expt using Rapid Prototyping Lens and IonCCD detection







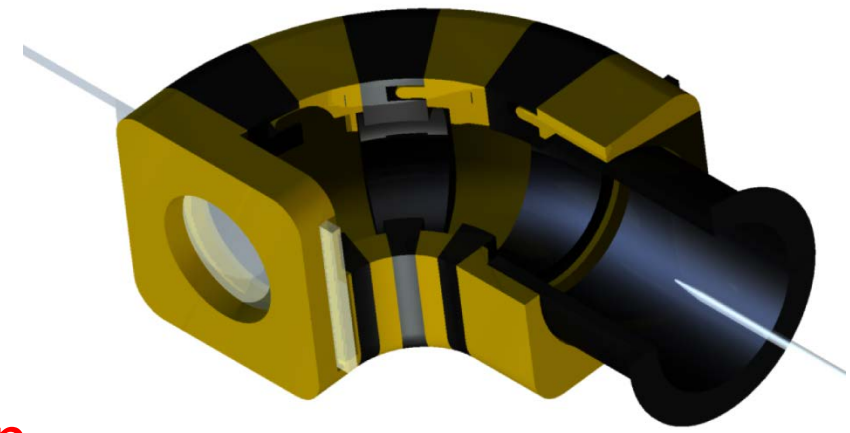
Ion acceptance region from simulation data

Zane Baird

MS entirely in air?

Ion generation: ambient ionization

Ion focusing: 3D printed lens systems



Transfer efficiency > 30 %
Spot size 500 µ

Ion separation: pulsed ion beams, ion mobility separation

Ionic reaction: ions cross a vapor stream and react

Ionic product collection: in amounts up to 300 mg

Ion detection: pixelated imaging detector (IonCCD, OI Analytical)

Summary

Tandem Mass Spectrometry

Quest for speed & simplicity in analyzing complex mixtures

Ambient Ionization

Quest for speed, simplicity & generality in making ions

Mini MS

Small, simple mass spectrometers, used anywhere

Chemical Synthesis by MS

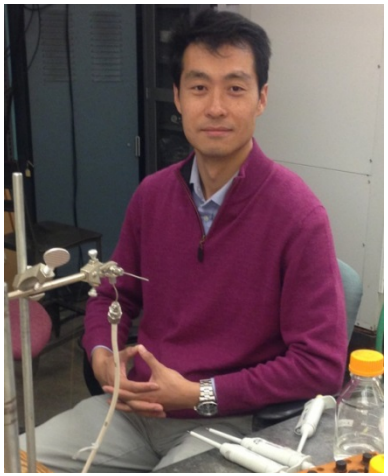
Ion deposition, reaction and synthesis

Acknowledgements

Thomas Mueller

Xin Yan

Xin Li



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Zane Baird

Nick Manlicke