Ion Mobility Spectrometry:
Analyzing Molecules as They Tumble through Life

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Outline

- What is ion mobility spectrometry (IMS)?
- What are the differences between the diverse IMS methods? (i.e. DTIMS, TWIMS, FAIMS, DMA, TIMS, etc.)?
- The benefits of using IMS
- Current and future IMS applications

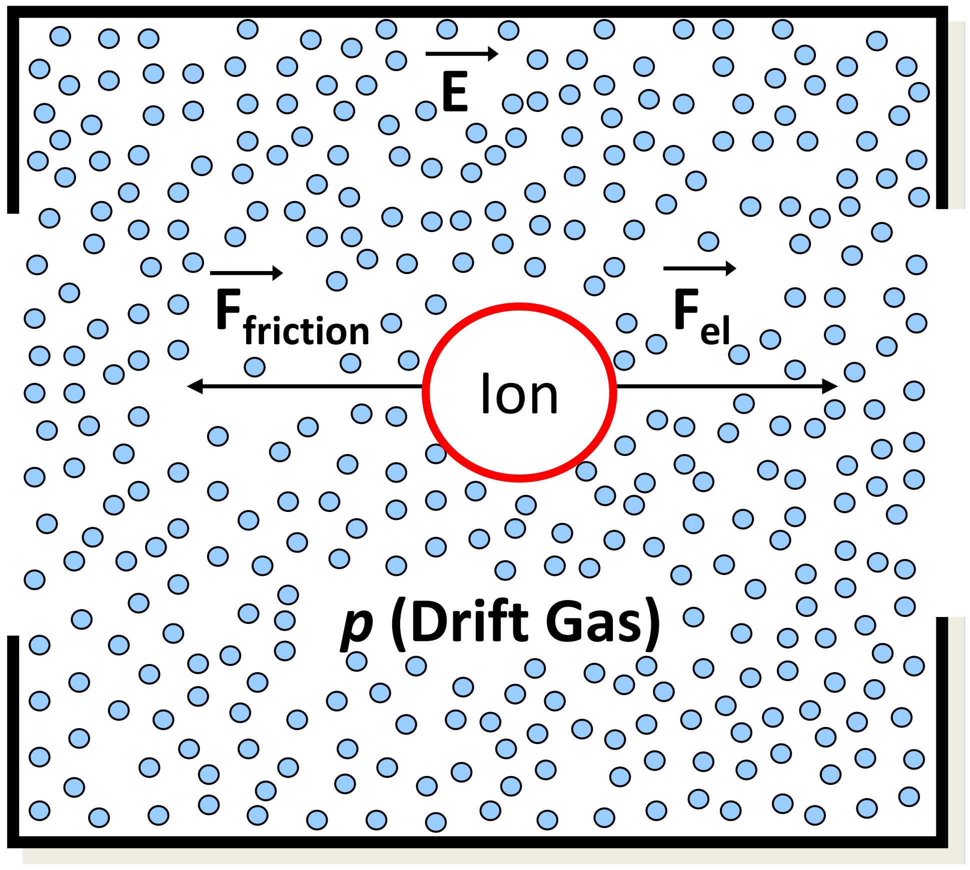
Have you been within 50 feet of an IMS device in the last 5 days?

IMS concept

- Defines how an ion drifts through a gas under the influence of an electric field

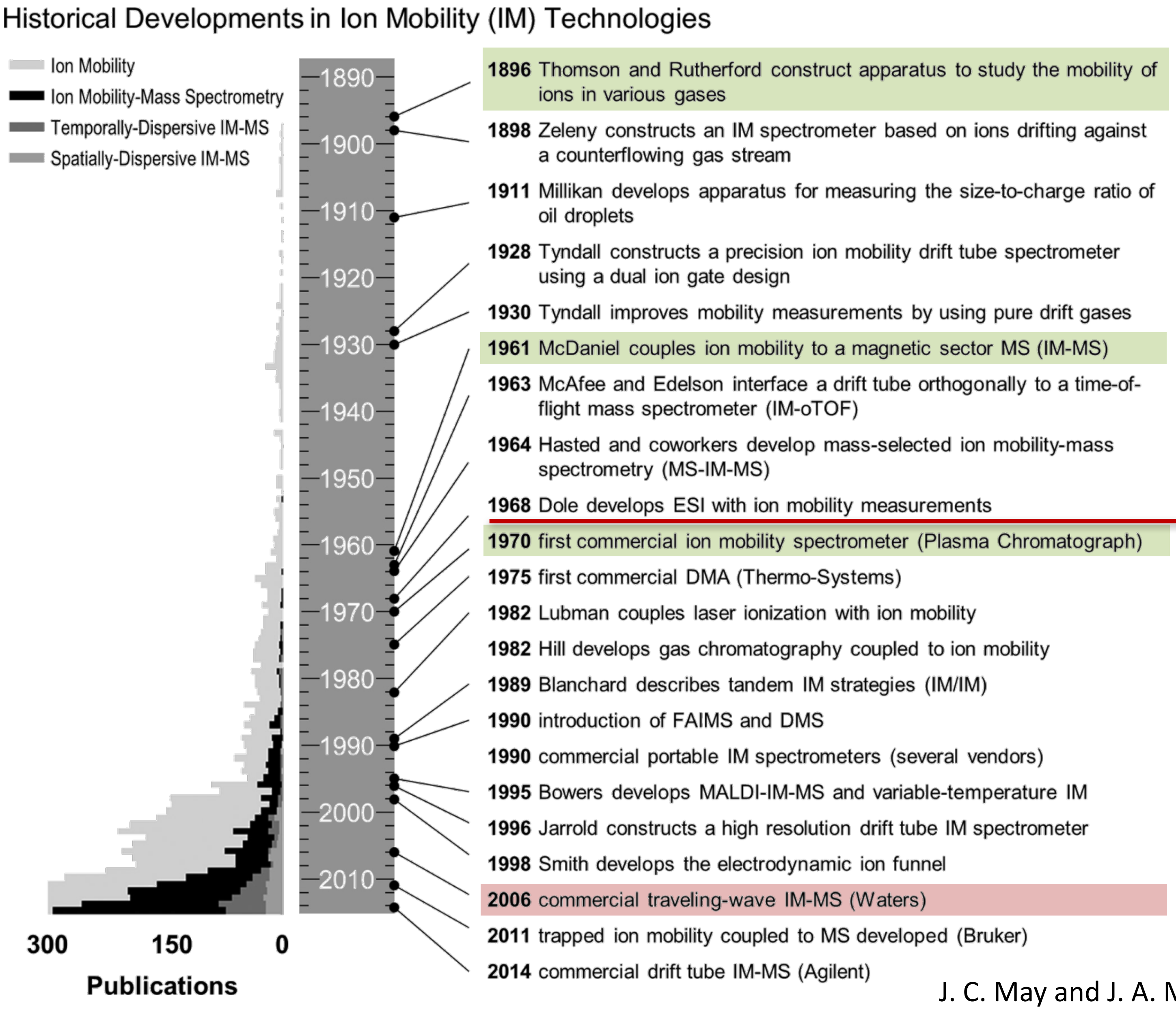
- Separation based on the mass, charge, size & shape

- Variables in diverse IMS methods
    1. Electric field
    2. Pressure
    3. Gas composition
    4. Gas flow
    5. Temperature



Drift Cell

Evolution of IMS



Deployment in the military

J. C. May and J. A. McLean, Analytical Chemistry 87, 1422-1436 (2015).

Charles "Steve" Harden

- Studied gas phase ion molecule reactions for Ph.D. research
- In 1967, he was placed on Active Duty at the Edgewood Arsenal - Army center for chemical warfare agent (CWA) research
- Harden's preparation was pivotal to the development and fielding of IMS-based nerve agent detectors in the 1970s and 80s

Slide courtesy of Abigail Eiceman

Trace warfare agent devices

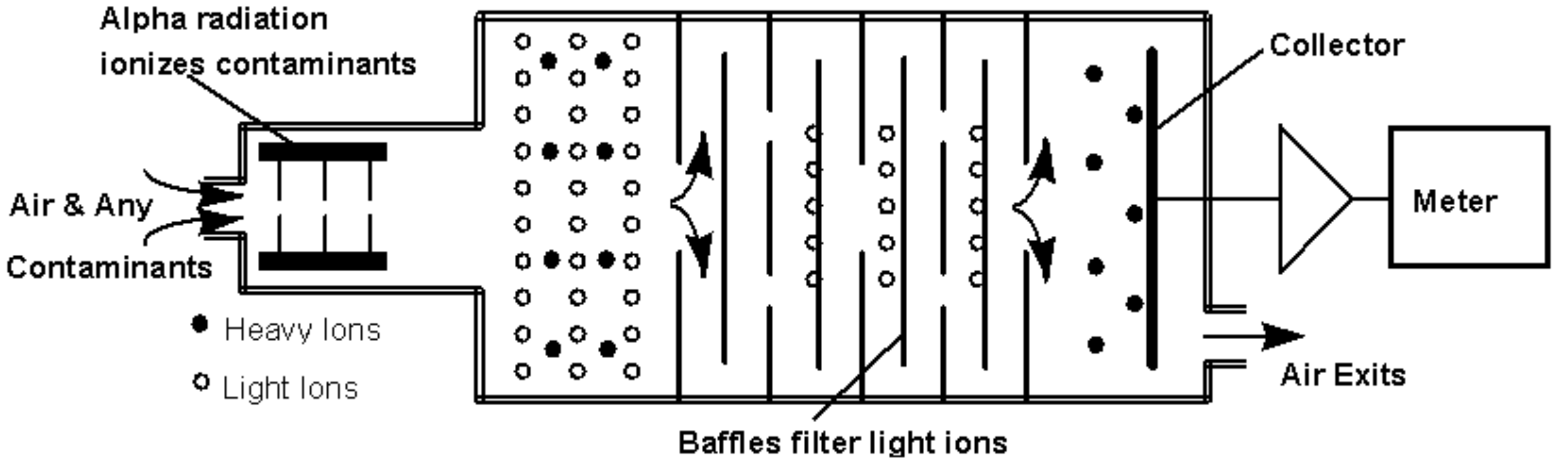
- Prior to the 1960s, the main CWA detection methods were colorimetric techniques or indicating paper tapes
- M8 Portable Automatic Chemical Agent Alarm was developed for continuous and automated detection of nerve agent vapors
- M8 was not sensitive to nerve agents or mustard gases
- The Army needed a more reliable, solution-free dry chemistry detector

Slide courtesy of Abigail Eiceman

Trace warfare agent devices

- In 1973, Harden linked atmospheric pressure ionization and the Honeywell ionization detector to create the M8A1

- Compact dry detector, no larger than a lunchbox replaced the M8



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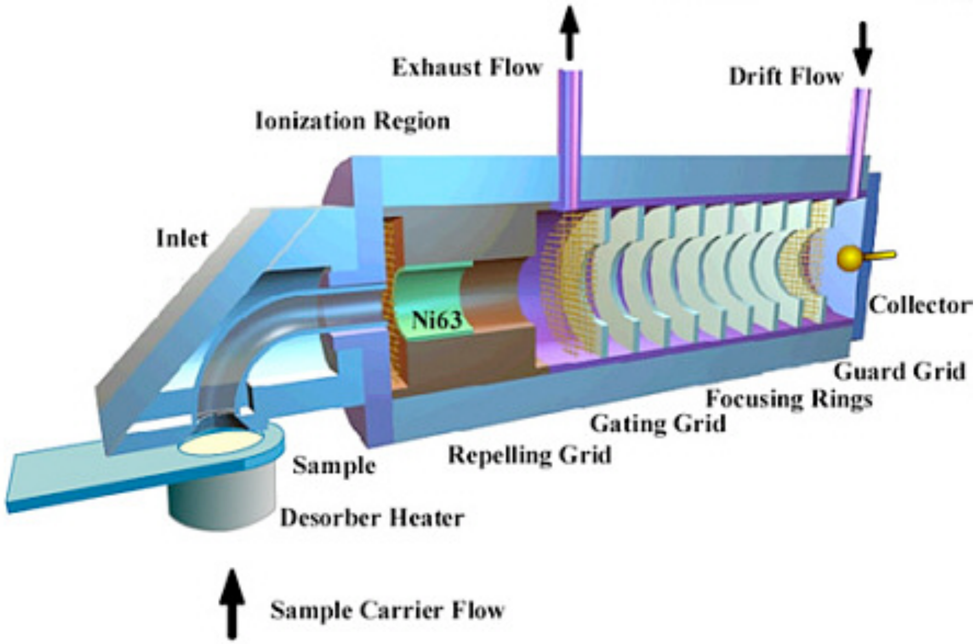
IMS in the military



- Current IMS devices: powerful for explosive and CWA detection
- Used for airport security, drug discovery, forensics, and customs
- Low detection limits and high sensitivity offered broader applications

What are the differences between the diverse IMS methods

(DTIMS, TWIMS, FAIMS, DMA, TIMS)?

If you say “I perform ion mobility spectrometry measurements”

- It is similar to saying “I drive a car”

What type of IMS?

Which buffer gas?

Which instrument do you use?

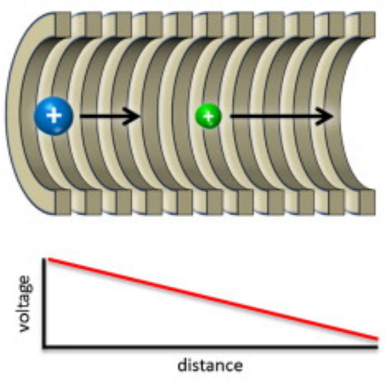
What is your resolving power?

What pressure?

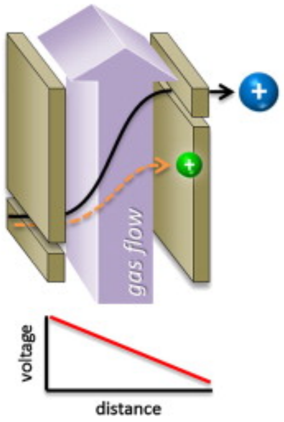
How rapid are your measurements?

Types of ion mobility spectrometers

- **<u>Static Fields</u>**
  1. Drift Tube IMS (DTIMS)
  2. Differential Mobility Analyzer (DMA)

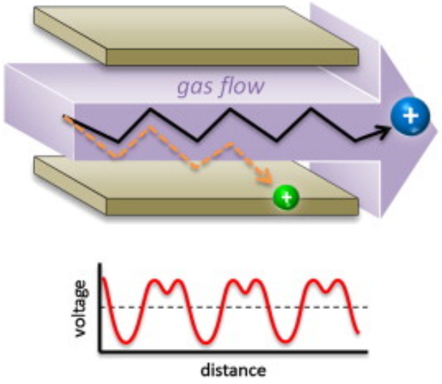


DTIMS

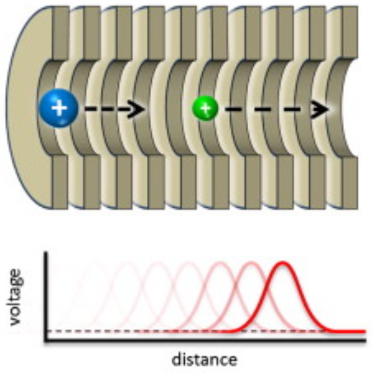


DMA

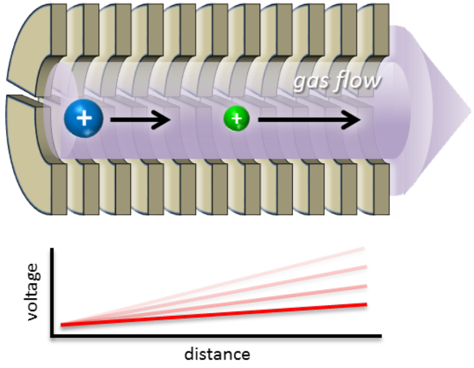
- **<u>Dynamic Fields</u>**
  1. Field Asymmetric IMS (FAIMS)
  2. Traveling Wave IMS (TWIMS)
  3. Trapped IMS (TIMS)



FAIMS



TWIMS

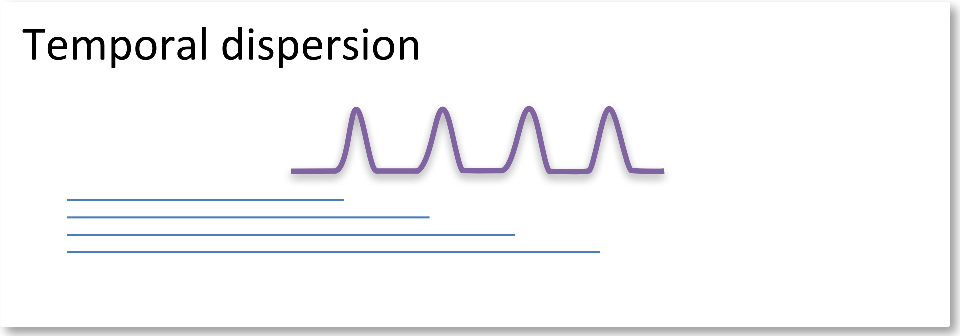


TIMS

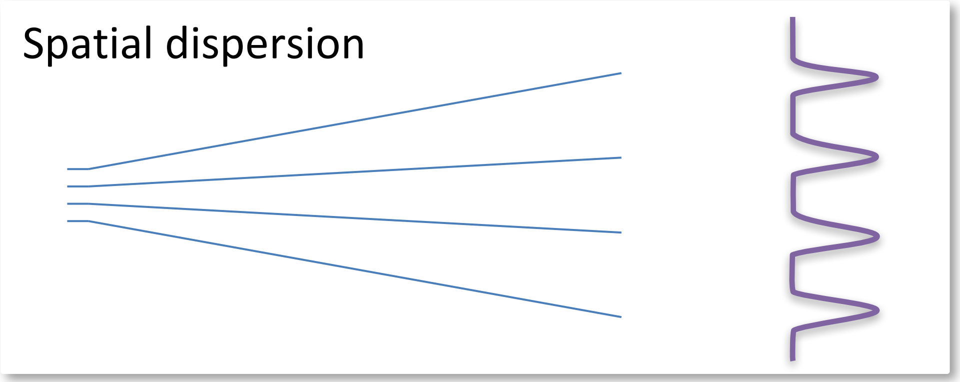
Biochimica et Biophysica Acta 1811, 935–945 (2011).

Types of ion mobility spectrometers

- **Temporal Separation**

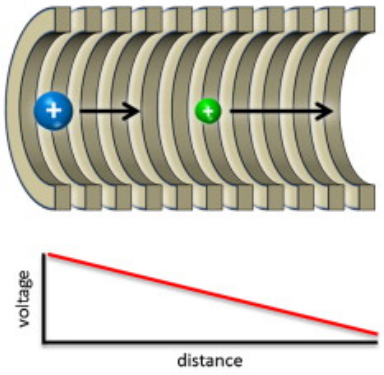


- **Spatial Separation**

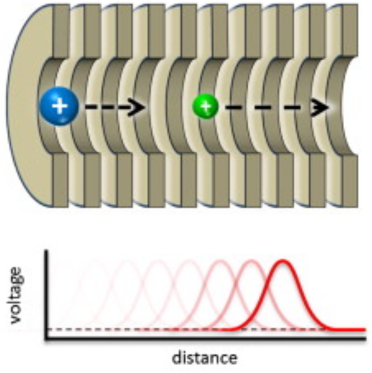


Types of ion mobility spectrometers

- **<u>Temporal Separation (All Ion Analysis)</u>**
  1. Drift Tube IMS (DTIMS)
  2. Traveling Wave IMS (IMS)

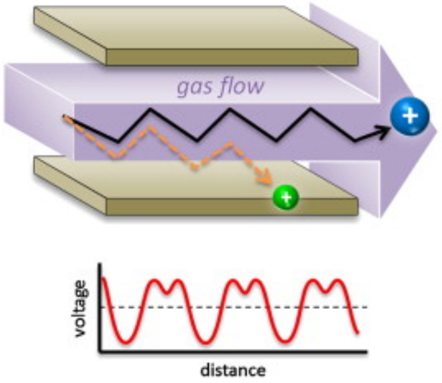


DTIMS

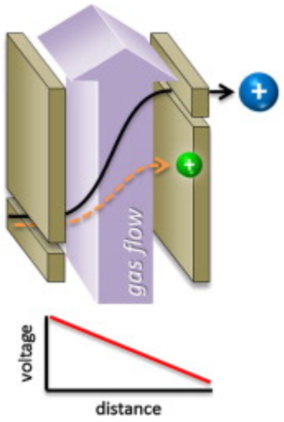


TWIMS

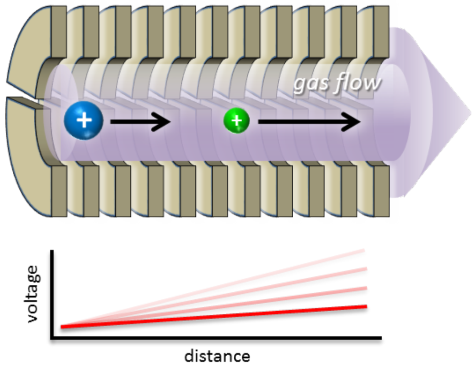
- **<u>Spatial Separation (Scanning Analysis)</u>**
  1. Field Asymmetric IMS (FAIMS)
  2. Differential Mobility Analyzer (DMA)
  3. Trapped IMS (TIMS)



FAIMS



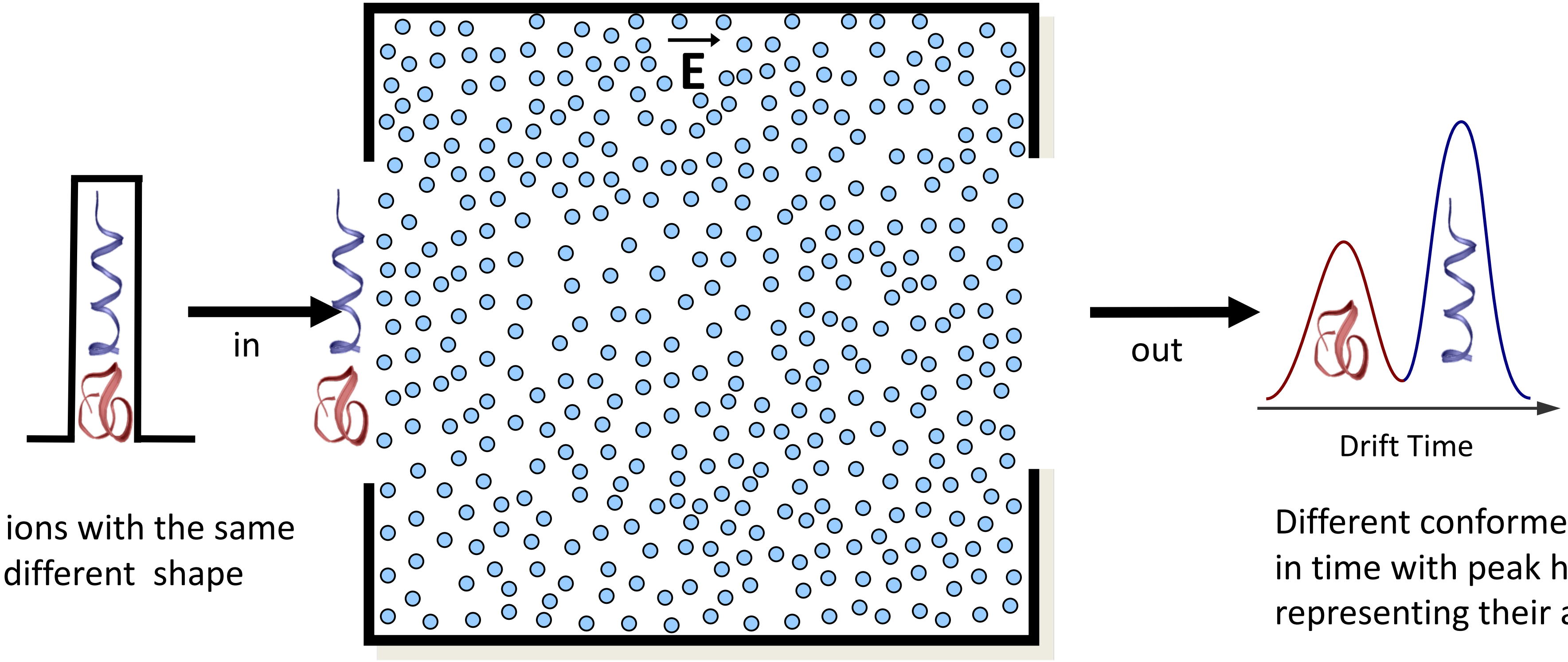
DMA



TIMS

Biochimica et Biophysica Acta 1811, 935–945 (2011).

Drift Tube IMS (DTIMS)



Pulse of 2 ions with the same m/z but a different shape

Drift Cell

Different conformers separate in time with peak heights representing their amounts

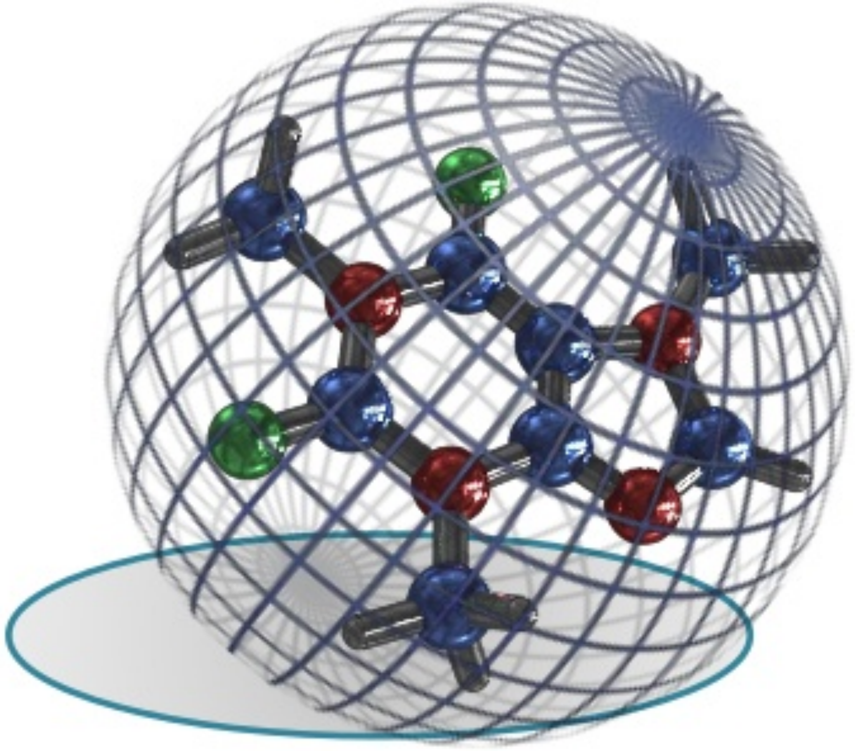
Constant Velocity

$v = K \vec{E}$

K = ion mobility

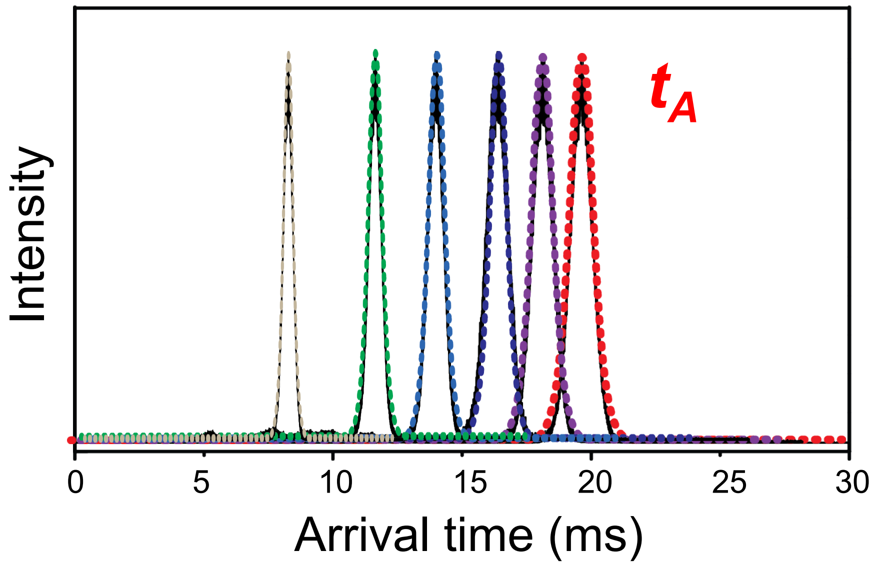
Ion-neutral collision cross section (CCS)

- Value related to the size and shape of an ion
  Corresponds to the area that collides with the drift gas
- Robust physicochemical property
- Can easily be compared between labs
- Varies depending on drift gas



Slide courtesy of Professor Kevin Pagel and Waters

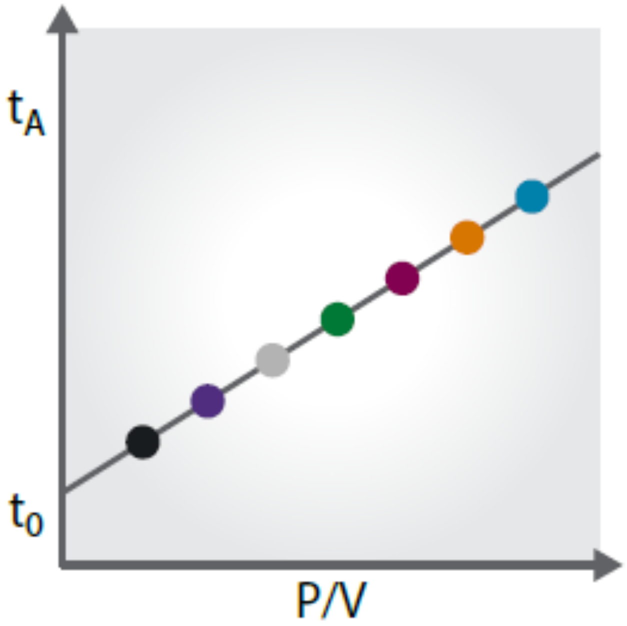
DTIMS – collision cross section (CCS) determination



Drift Voltage	t_A
50 V	19 ms
55 V	18 ms
60 V	16 ms
70 V	14 ms
100 V	11 ms
150 V	8 ms

Slide courtesy of Professor Kevin Pagel

DTIMS – collision cross section (CCS) determination



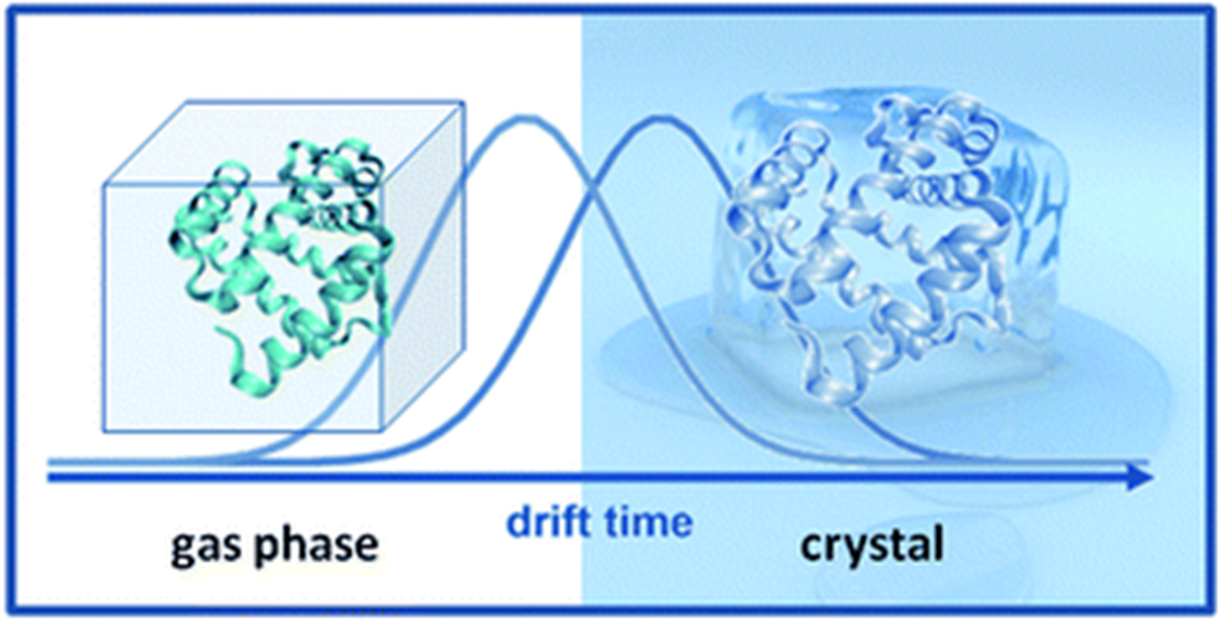
$$y = A\,x + B$$

$$t_A = \frac{L^2}{K_o}\left(\frac{273.15}{760\,T}\right)\left(\frac{p}{V}\right) + t_0$$

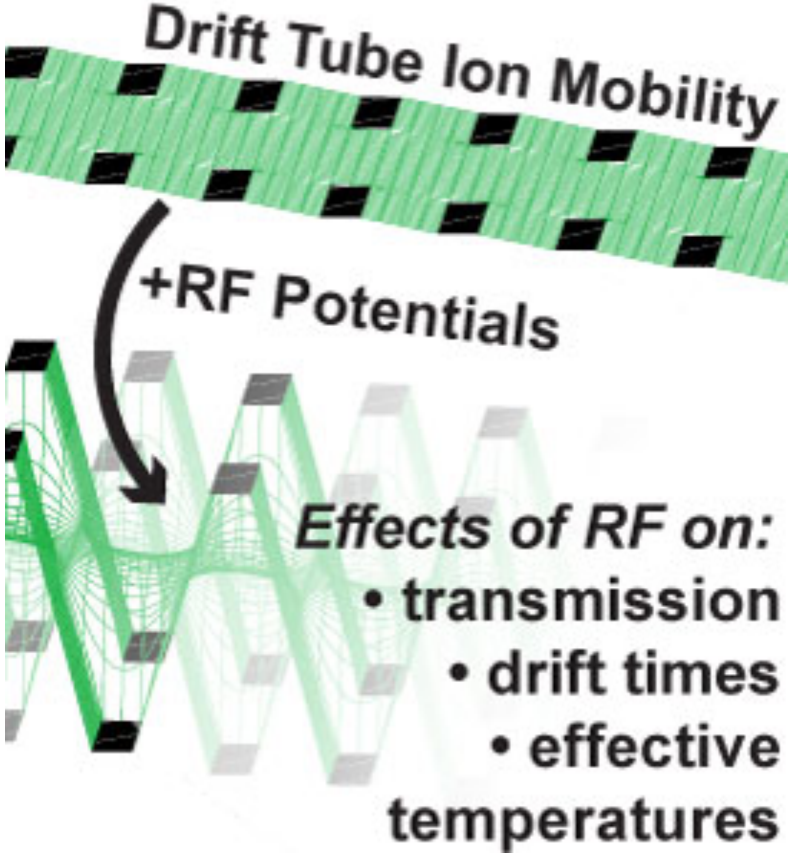
Mason-Schamp Equation

$$CCS = \Omega = \frac{3\,q}{16\,N}\left(\frac{2\,\pi}{\mu\,k_B\,T}\right)^{1/2}\frac{1}{K_0}$$

Utility of accurate CCS measurements



E. Jurneczko, P.E. Barran. *Analyst.* **2011**, 136, 20–28.



S.J. Allen, M.F. Bush. *J. Am. Soc. Mass Spectrom.* **2016**, *27*, 2054–2063.

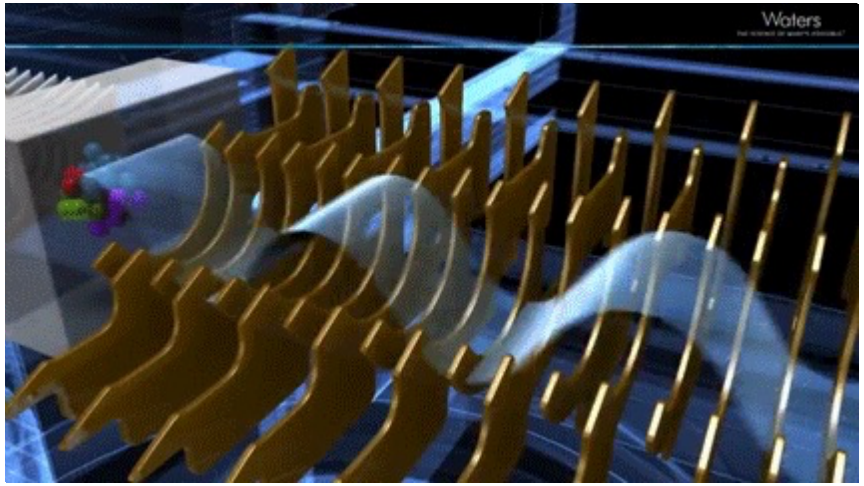
Skiing analogy

Drift Tube IMS
DTIMS

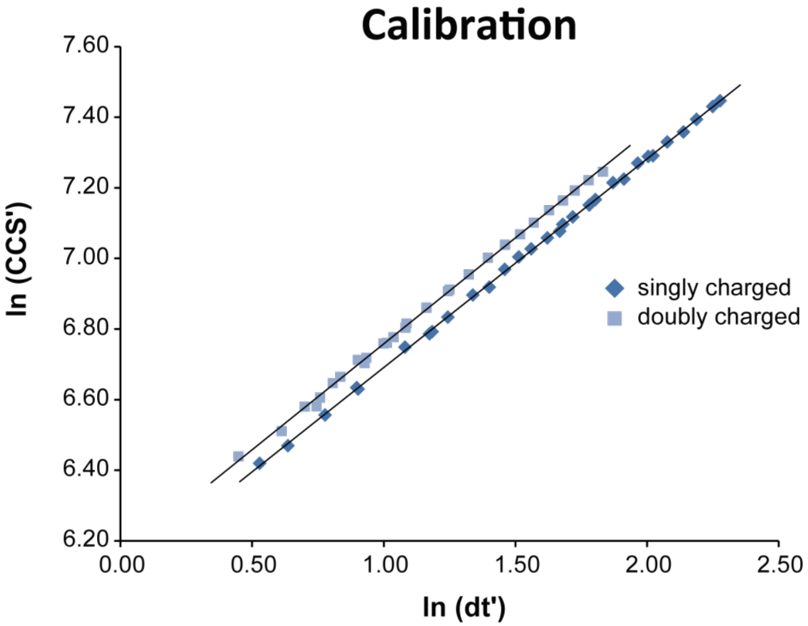
Traveling Wave IMS
TWIMS

TWIMS is based on a dynamic electric field

- Calibration needed to estimate TWIMS CCS values
- Calibrant and analyte ions should be of the same molecular type



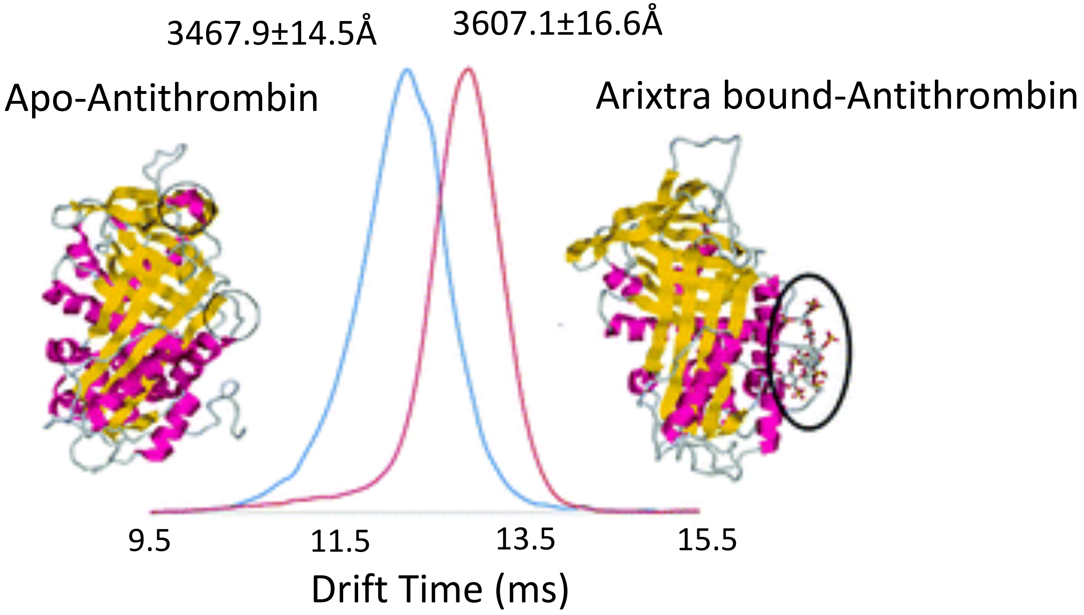
www.youtube.com/user/WatersCorporation



For details and spreadsheet visit: www.bcp.fu-berlin.de/chemie/pagel

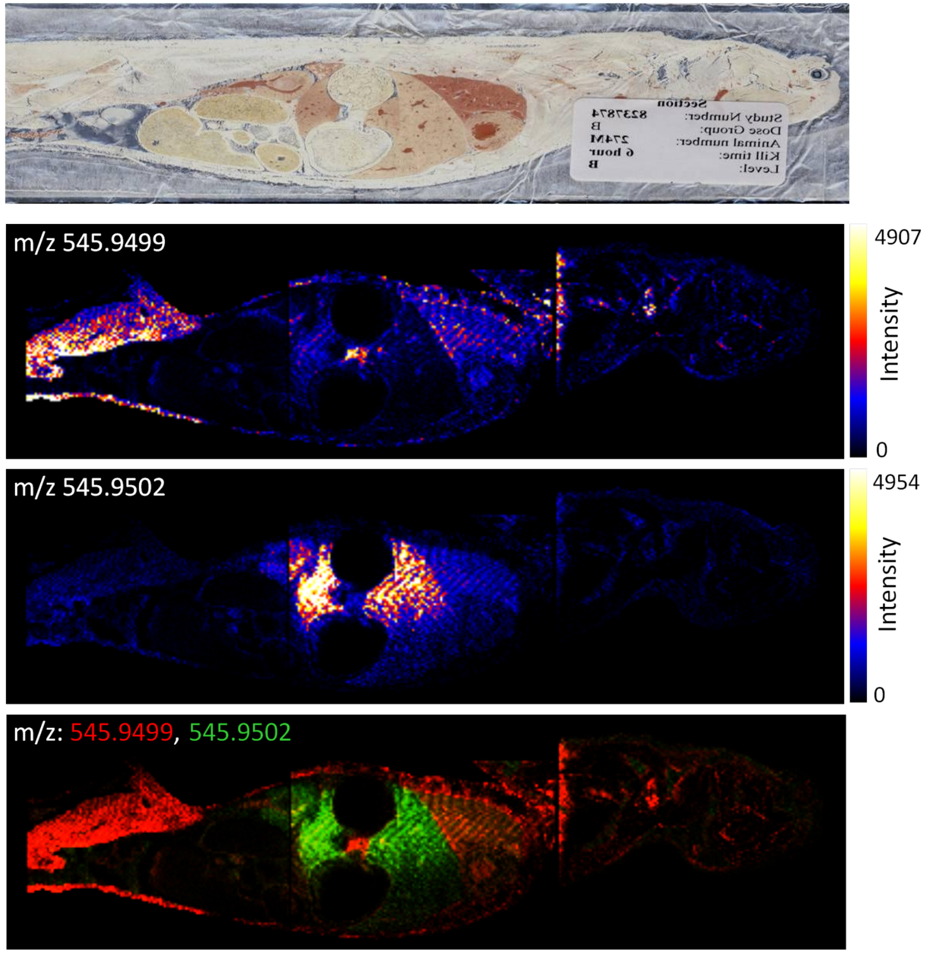
Slide courtesy of Professor Kevin Pagel

Utility of TWIMS measurements



Y. Zhao, et al. Analyst. **2015**, 140, 6980–6989.

Longitudinal, sagital section of whole body rat

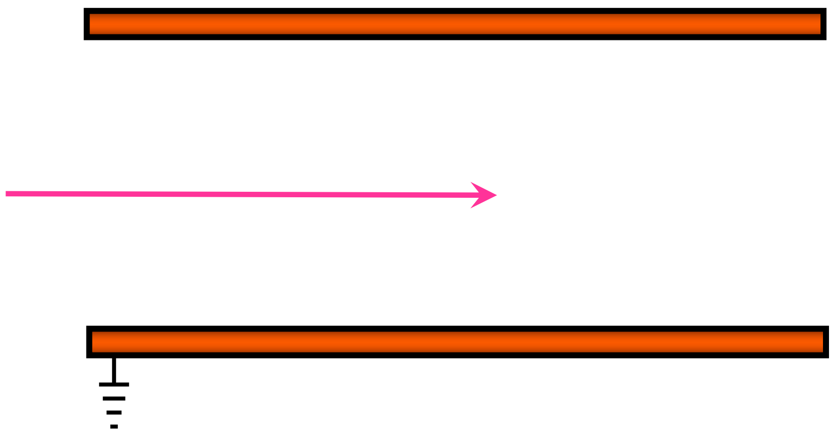


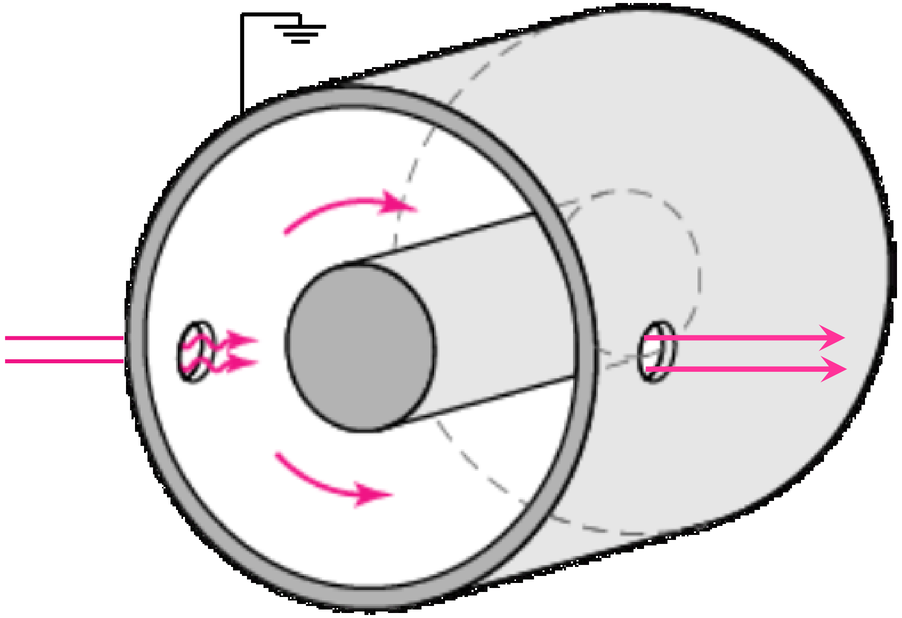
*Sample courtesy of Dr. Lars Bendahl

Data courtesy of Dr. Kevin Giles

Field Asymmetric IMS (FAIMS)

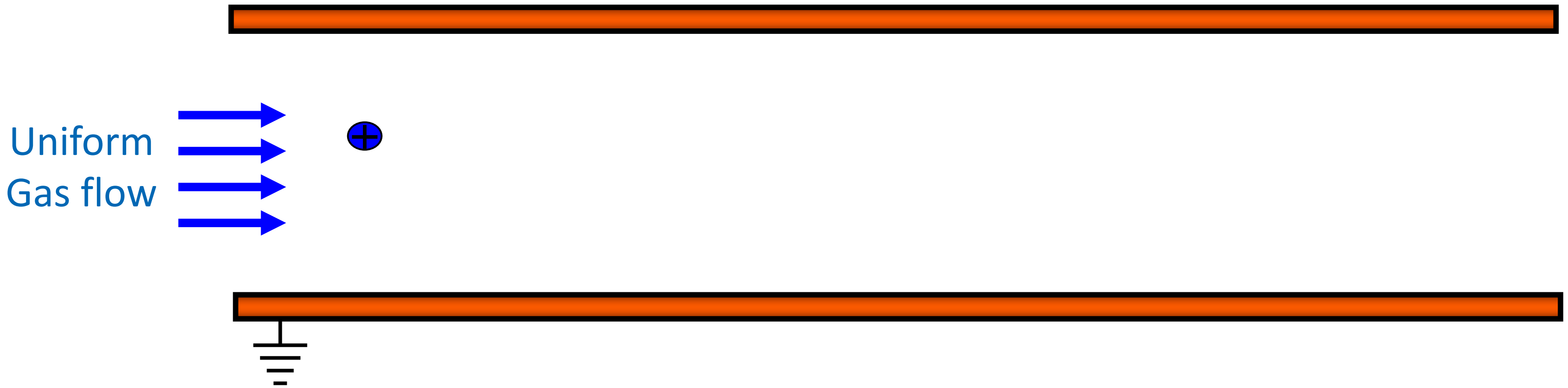
- Also known as **Differential Mobility Spectrometry (DMS)** or **Differential Ion Mobility Spectrometry (DIMS)**
- Separation based on the difference in an ion's mobility at low and high electric fields
- Performed either between plates or cylindrical electrodes





Slide courtesy of Drs. Susan Abbatiello and Michael Belford

FAIMS Separations



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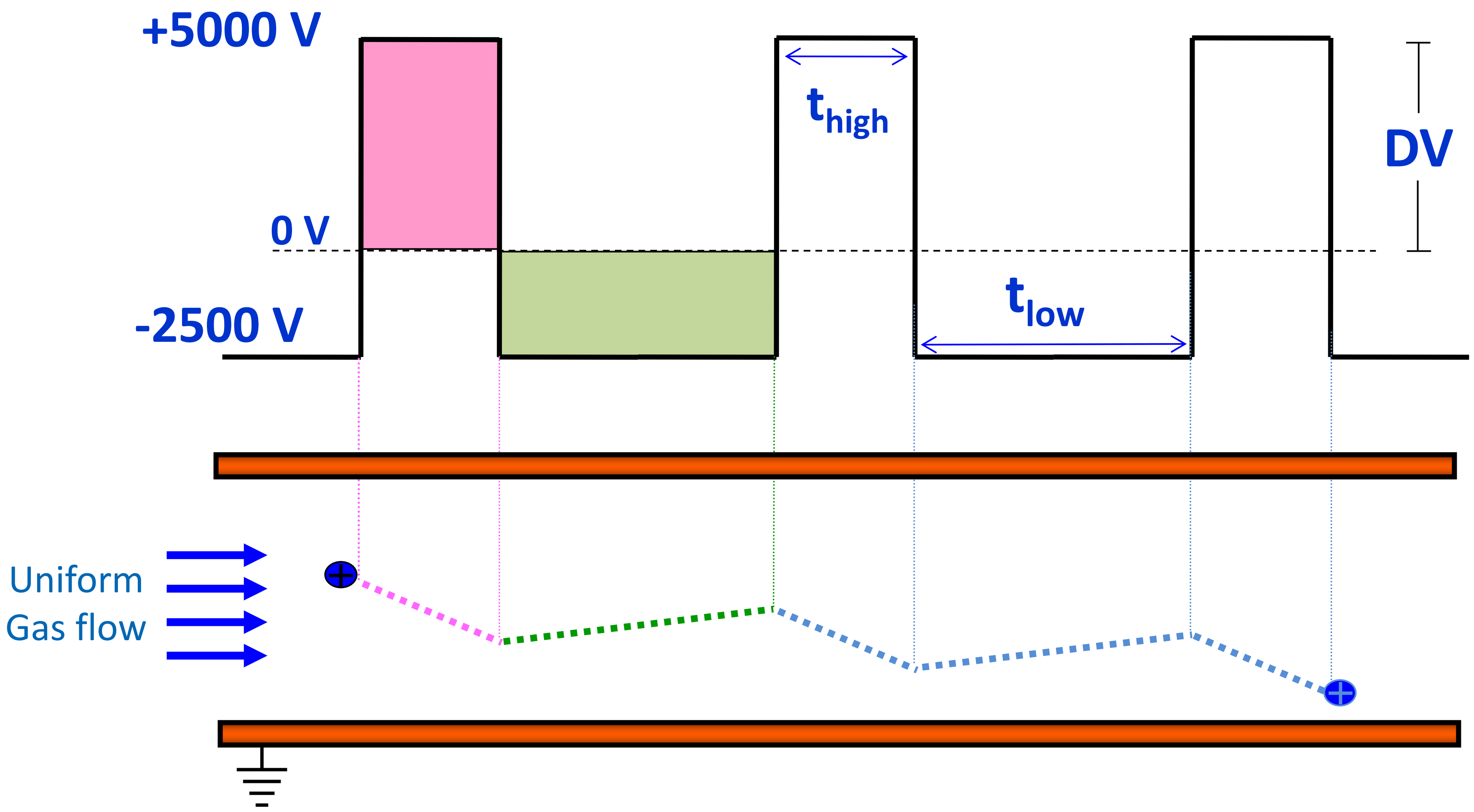
FAIMS Separations

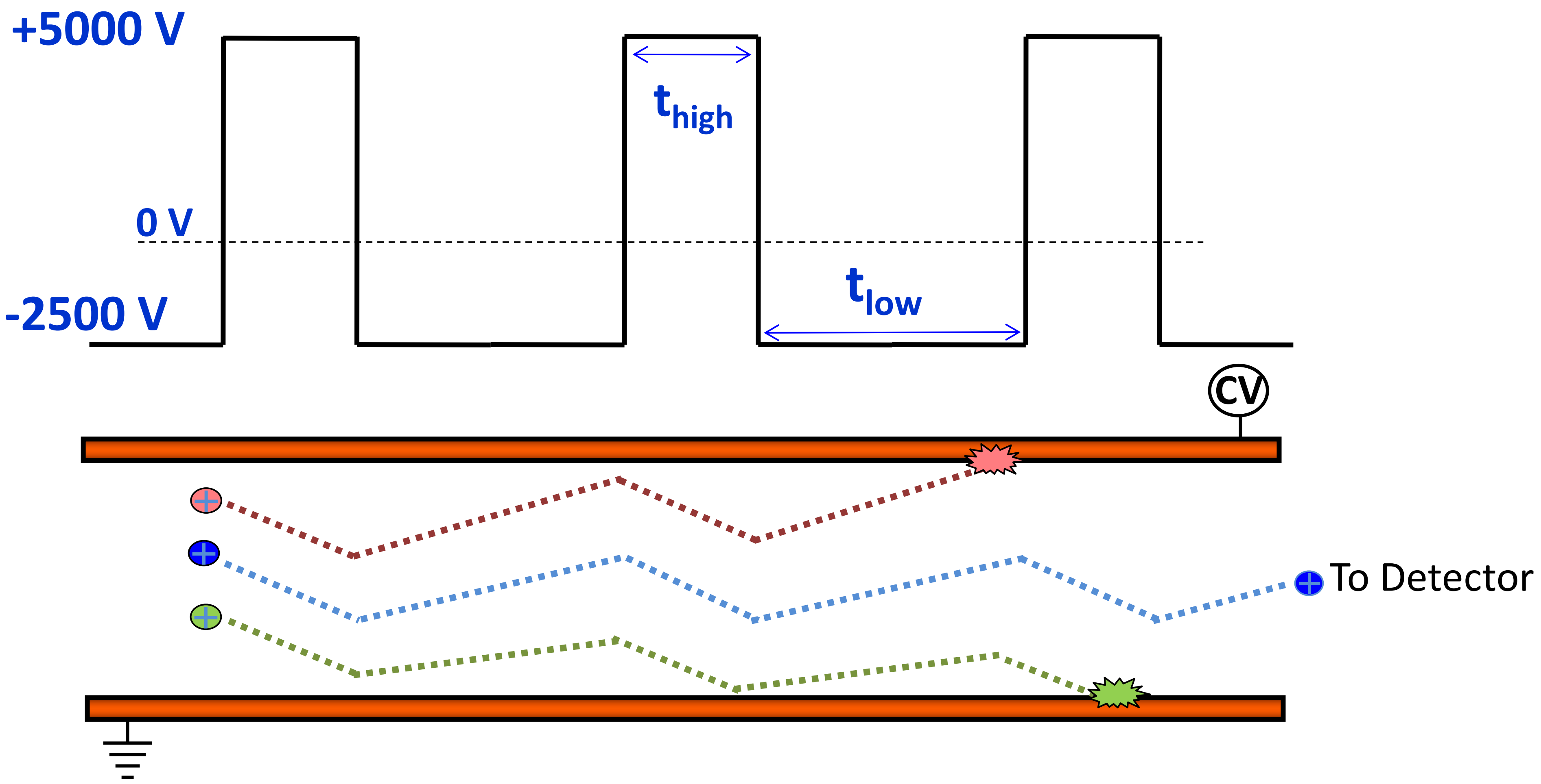
Ions are displaced using a dispersion voltage (DV)



Slide courtesy of Drs. Susan Abbatiello and Michael Belford

FAIMS Separations

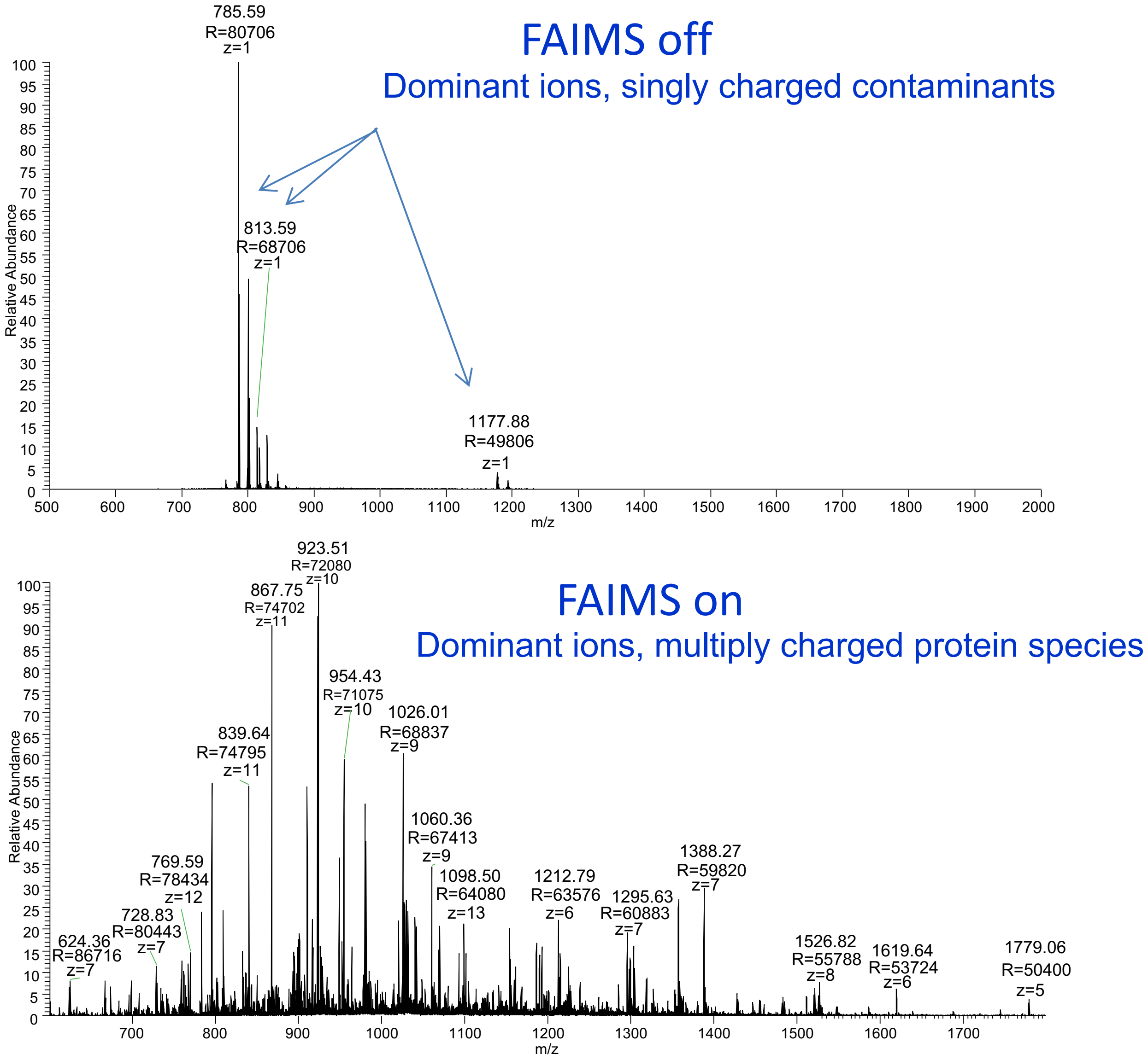
Ions are <u>targeted</u> using a compensation voltage (CV)



https://yost.chem.ufl.edu/research/faims/

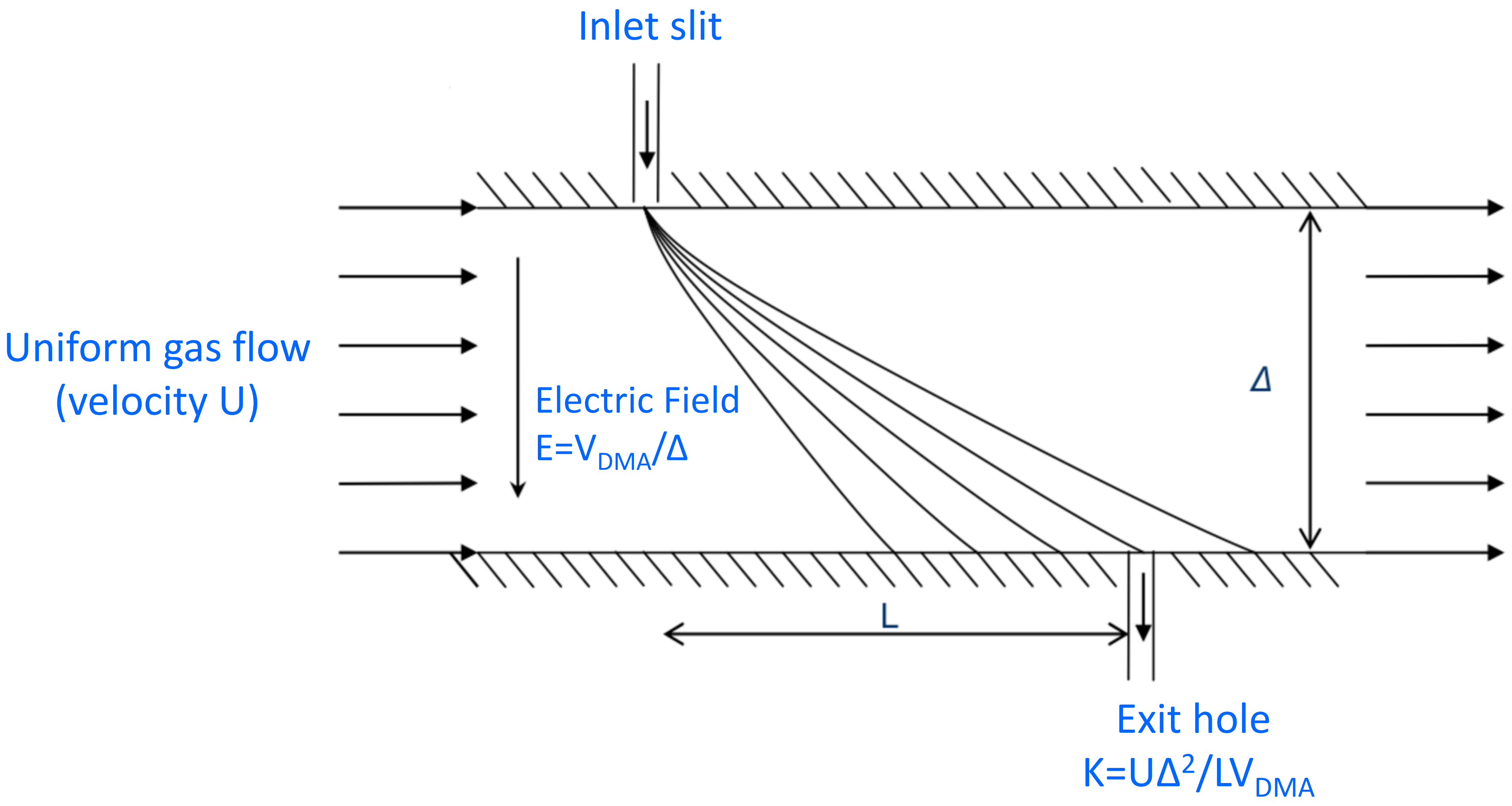
FAIMS operation and applications

- FAIMS operates at atmospheric pressure
- Has a narrow band filter so you must scan over CVs to acquire all ions
- Measured mobilities cannot be directly correlated to an ion's structure



Slide courtesy of Dr. Susan Abbatiello

Differential Mobility Analyzer (DMA)



Slide courtesy of Mario Amo Gonzalez and Professor Juan de la Mora

DMA Applications

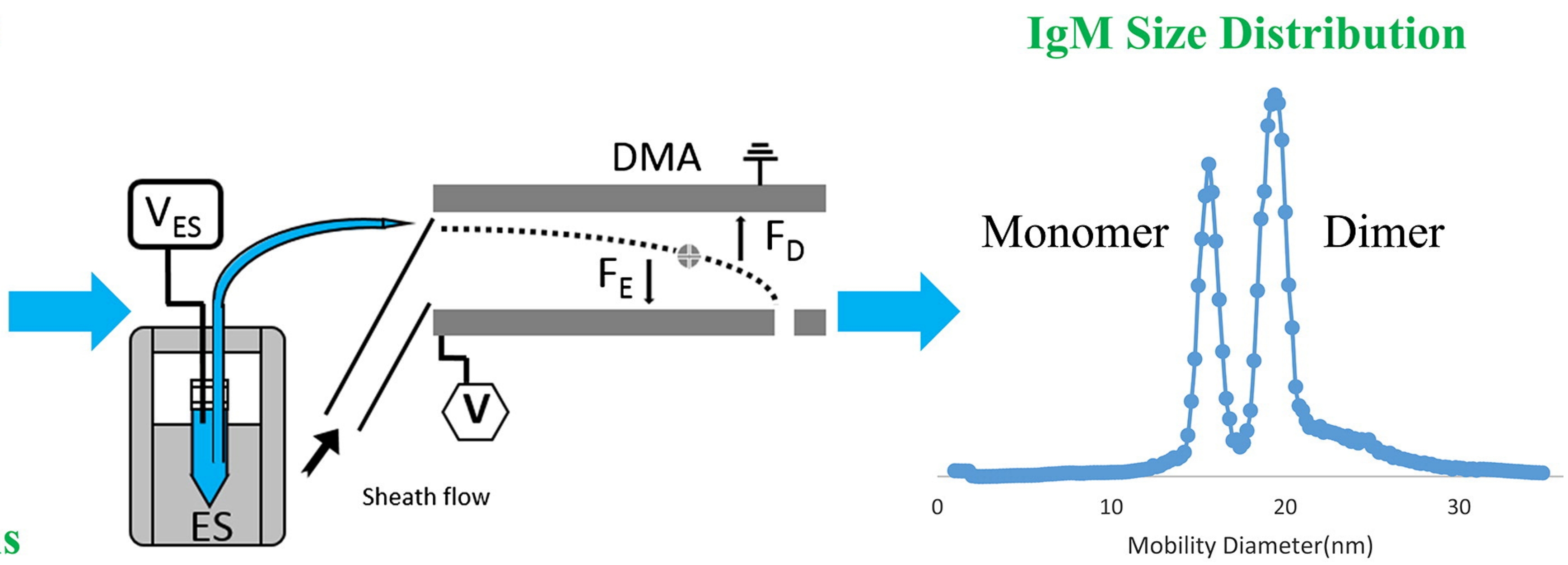
- Can analyze large particles
- DMA mobilities are directly related to structure
- Must scan over mobilities to acquire all ions

Lipoproteins

Viruses

Amyloids

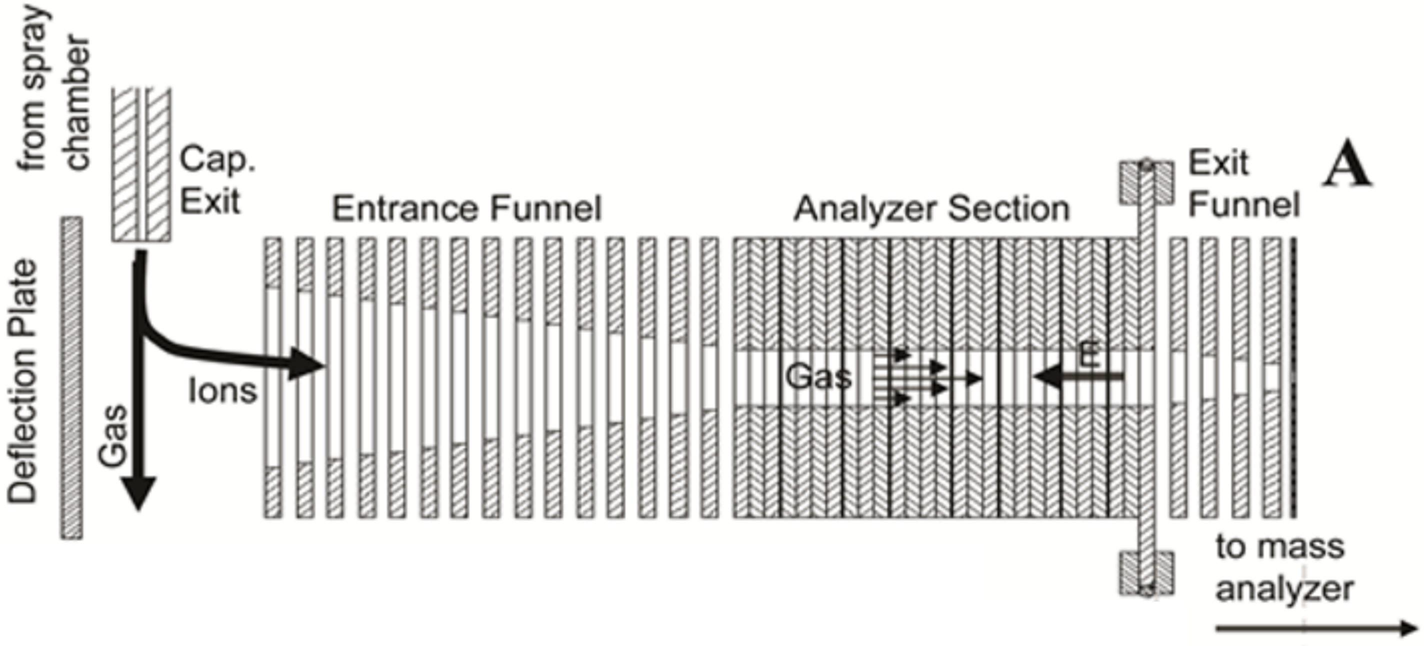
Glycoproteins



L. F. Pease, Y.-H. Tseng , Nanomedicine: Nanotechnology, Biology and Medicine, 10, 1591–1600 (2014).

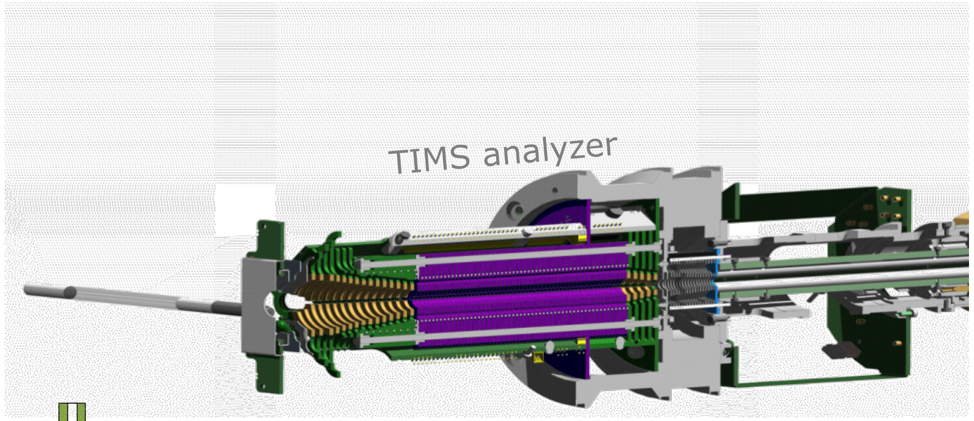
Trapped IMS (TIMS)

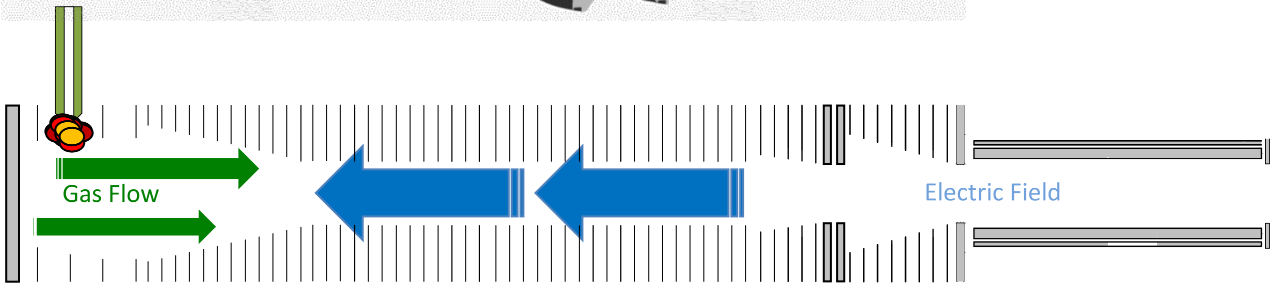
- Funnel-based device
- Ions accumulate in analyzer section
- Must scan over mobilities to acquire all ions
- Calibration required to get CCS values



M.E. Ridgeway, J.J. Wolff, J.A. Silveira, C. Lin, C.E. Costello, M.A. Park, Int. J. Ion Mobil. Spectrom. 2016, 1-9.

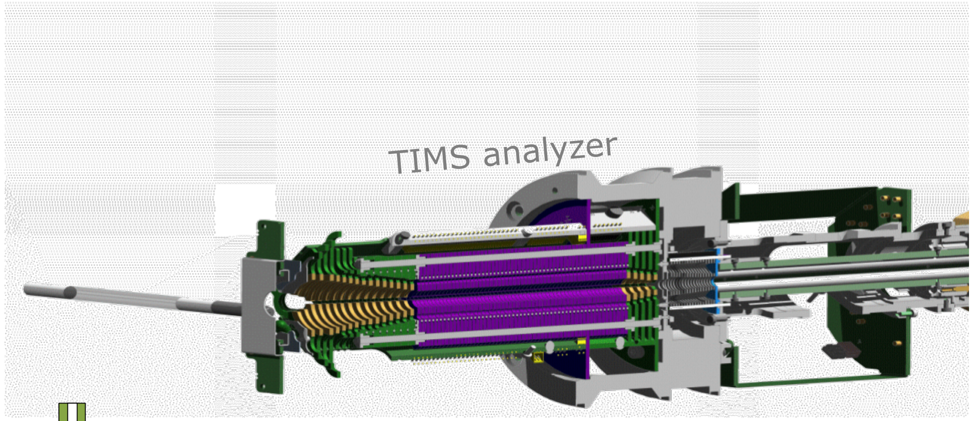
TIMS Operation

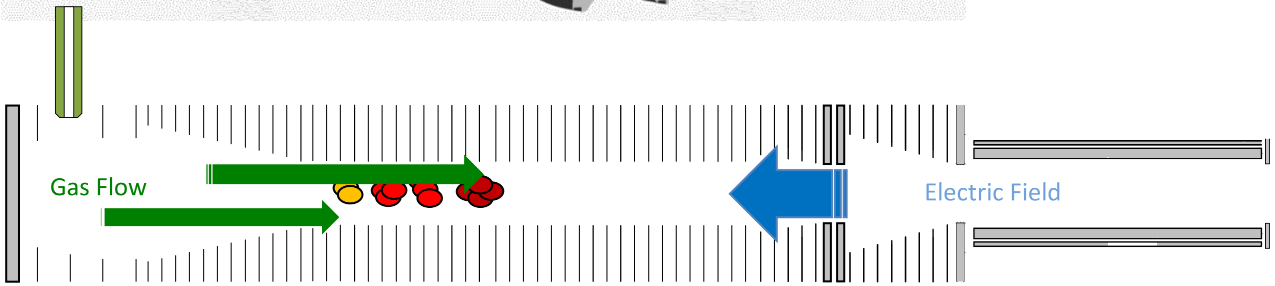




Slide courtesy of Dr. Lucy Woods

TIMS Operation





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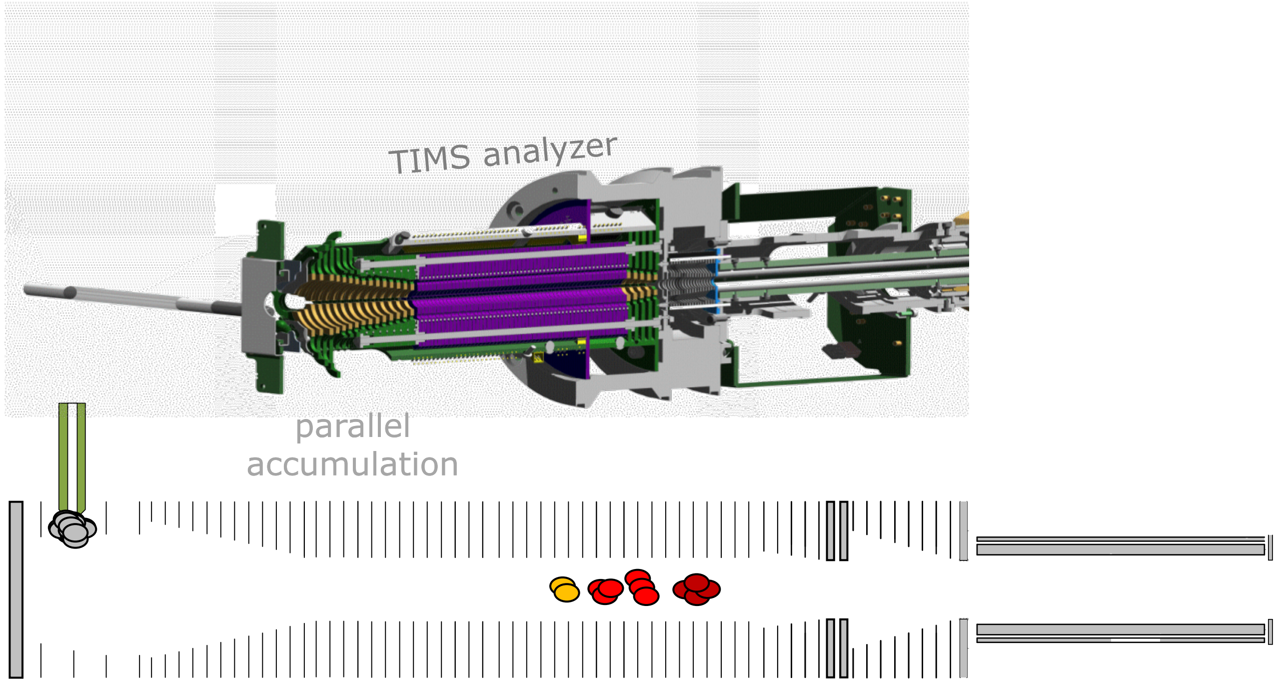
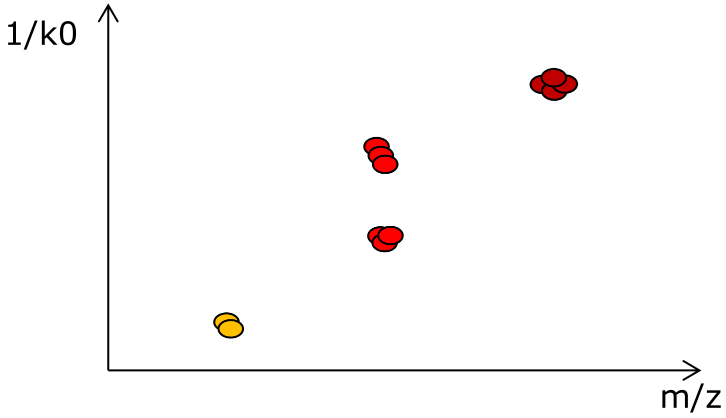
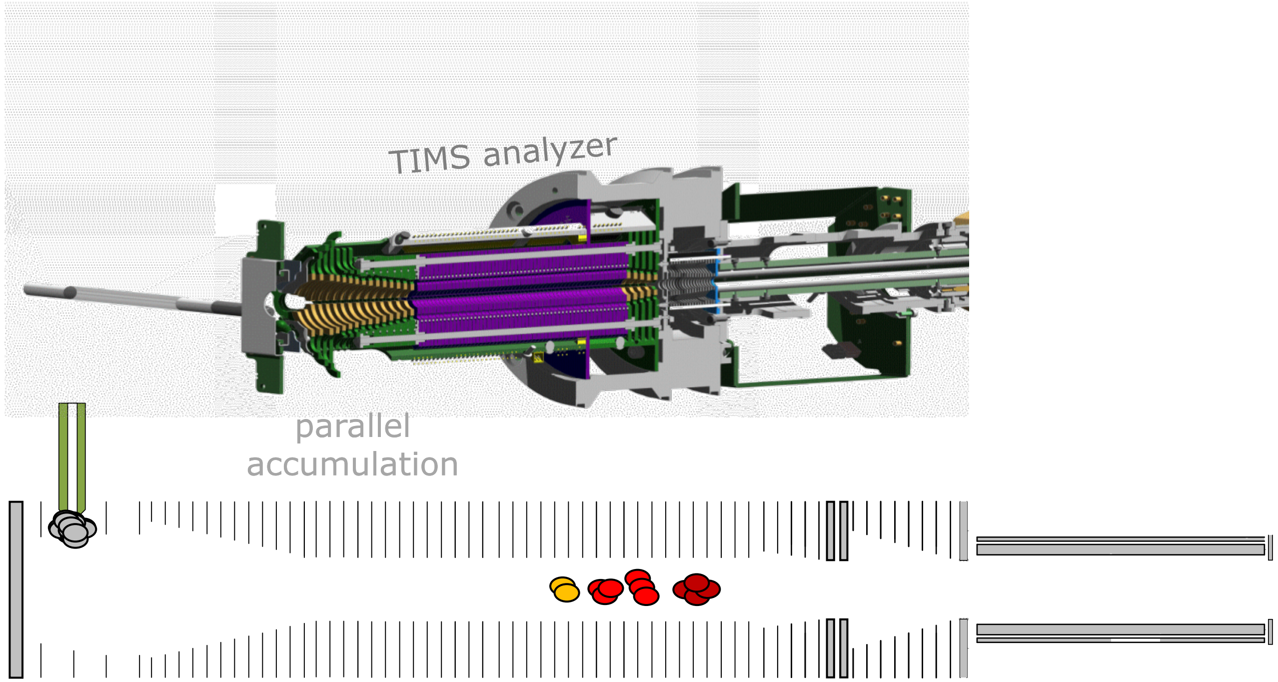
TIMS Operation

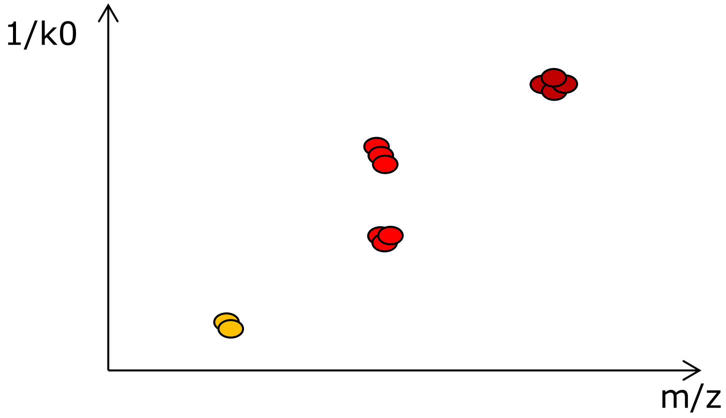




Slide courtesy of Dr. Lucy Woods

TIMS Operation





Slide courtesy of Dr. Lucy Woods

Skiing analogy

DTIMS

TWIMS

DMA

FAIMS (low field)

FAIMS (high field)

TIMS

IMS coupled with MS

Ion Mobility Spectrometers

- DTIMS
  - > 760 Torr
  - 760 Torr
  - < 760 Torr
- TWIMS
- FAIMS
- DMA
- TIMS

Mass Spectrometers

- Quadrupole
- Time-of-flight
- Trapping instruments (Orbitraps & FTICRs)

Commercially available IMS devices

Non-exhaustive list of companies selling IMS devices:

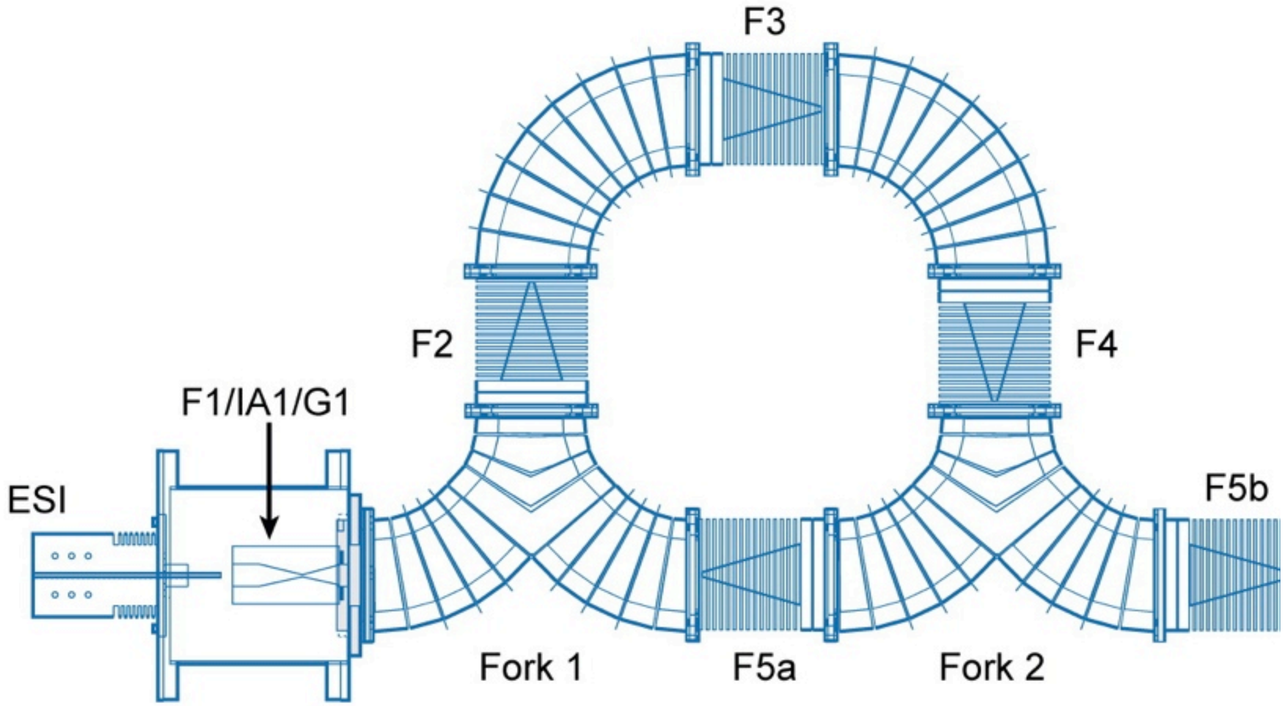
▪ AB Sciex	DMS	www.absciex.com
▪ Agilent	DTIMS	www.chem.agilent.com
▪ Bruker Daltonics	TIMS/DIMS	www.bruker.com
▪ Excellims	DTIMS	www.excellims.com
▪ Owlstone	FAIMS	www.owlstonenanotech.com
▪ Thermo Scientific	FAIMS	www.thermo.com
▪ TOF-Werk	DTIMS	www.tofwerk.com
▪ Waters Co.	TWIMS	www.waters.com

Noncommercial Devices – Cyclic IMS

- Cyclic DTIMS Instrument
- Resolution limited by mobility differences:
  → "The ATD bites its tail"
  → Avoid by ejecting unwanted ions

Current record:

100 cycles ~ 183 meter
~ 1.2 seconds



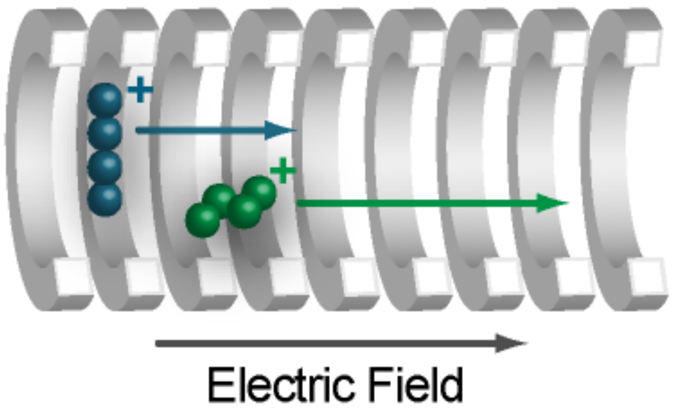
Clemmer group; Analytical Chemistry , 2009, *81*, 1482–1487

Slide courtesy of Professor Kevin Pagel

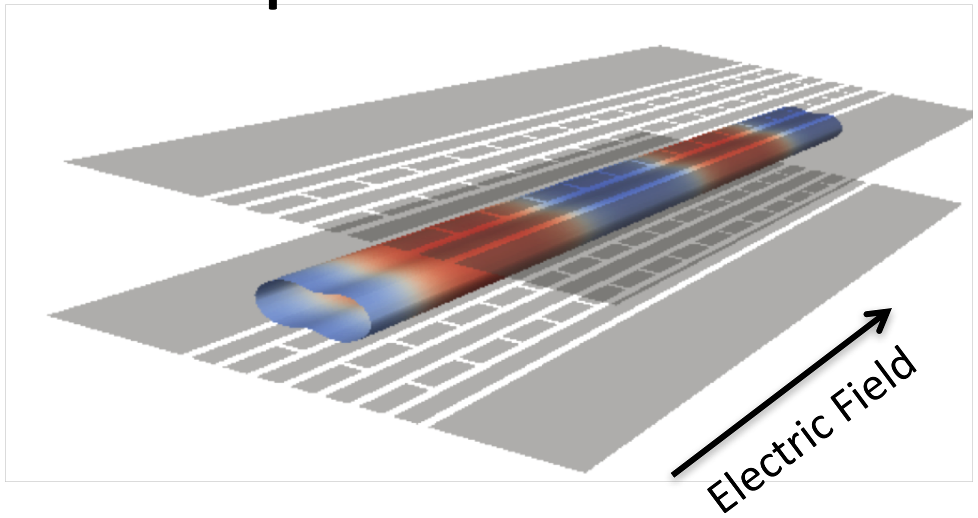
Noncommercial Devices – Serpentine IMS

- Convert ring-based lenses to parallel surfaces using Structures for Lossless Ion Manipulations (SLIM)

Ring-based lenses

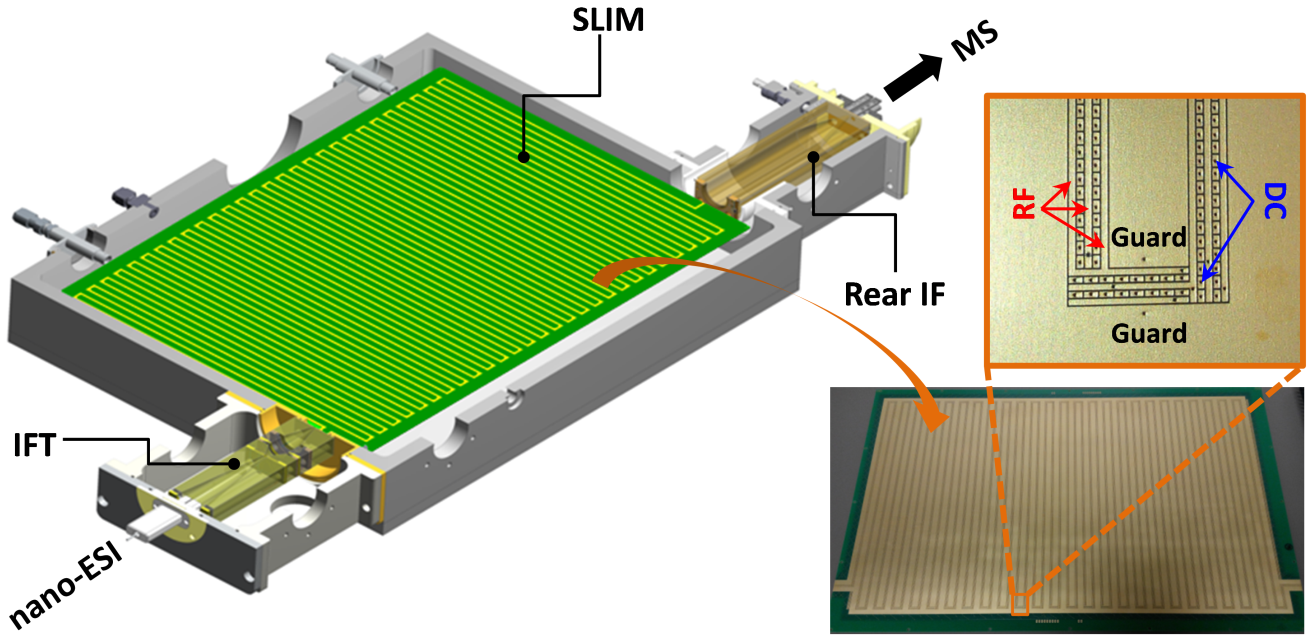


Electrode pattern on 2 parallel surfaces



Noncommercial Devices – Serpentine SLIM IMS

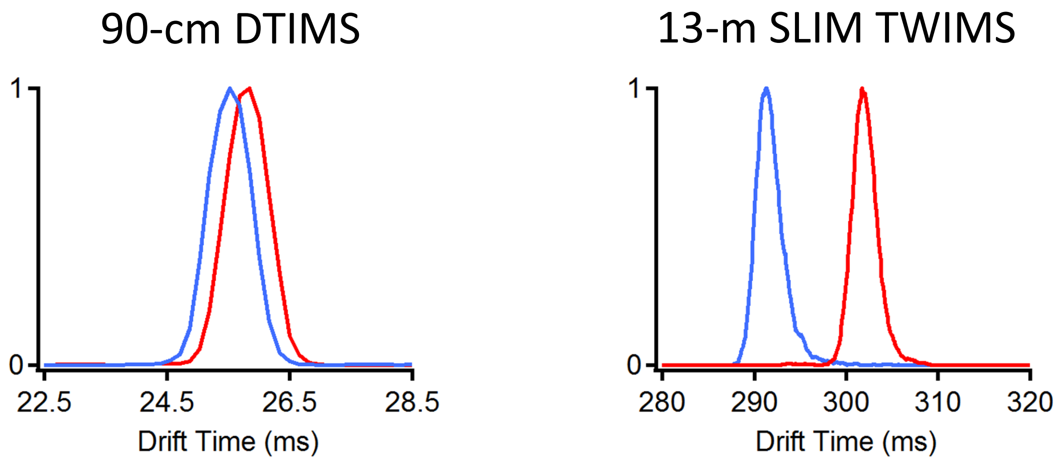
- Long path separations are performed in a small chamber
- Resolution not restricted to mobility differences
- Multilevel devices allow even greater resolution



Reverse Peptide Sequences

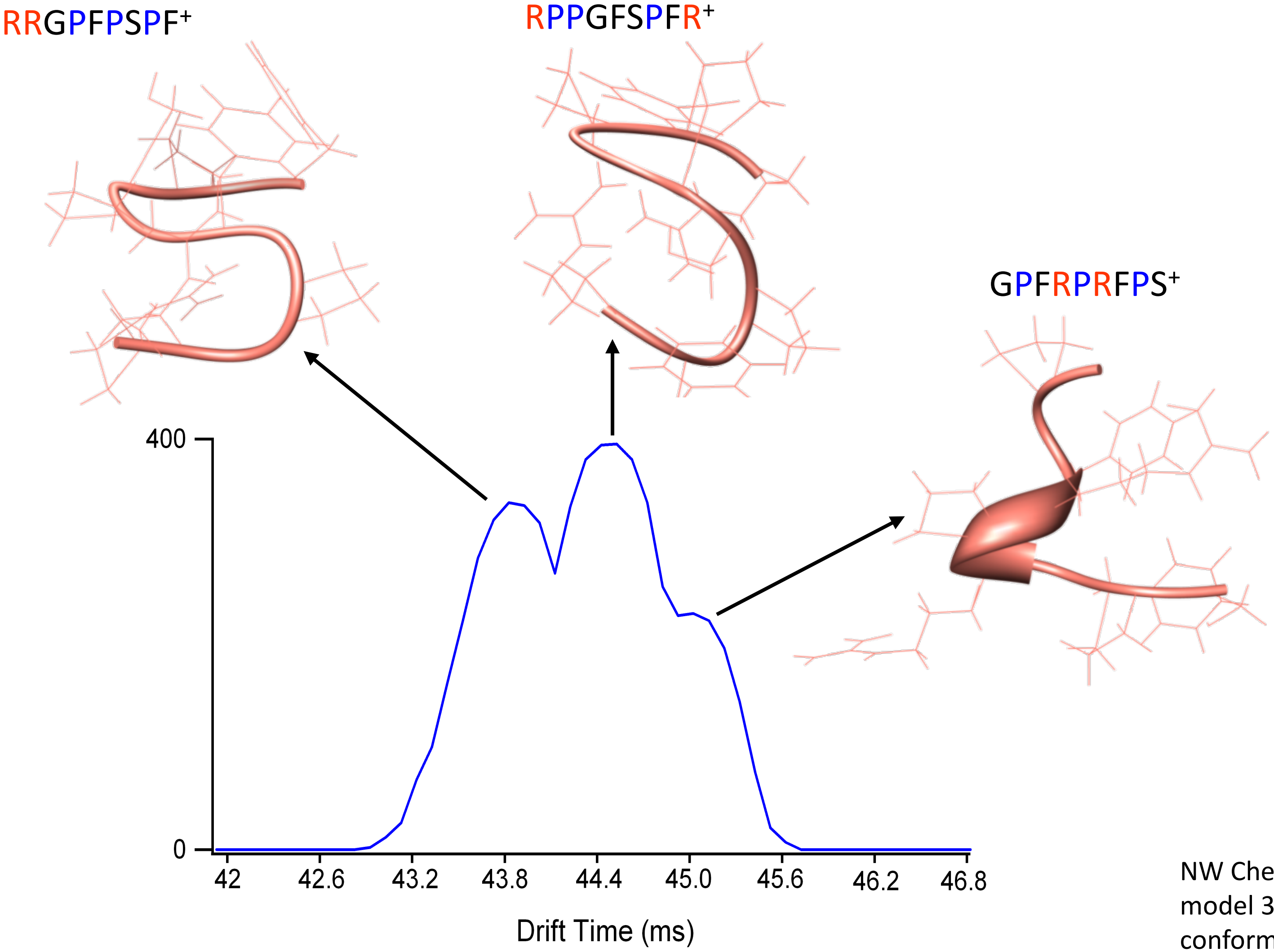
(Ser-Asp-Gly-Arg-Gly + H)$^+$ = 204 Å^2

(Gly-Arg-Gly-Asp-Ser + H)$^+$ = 206 Å^2



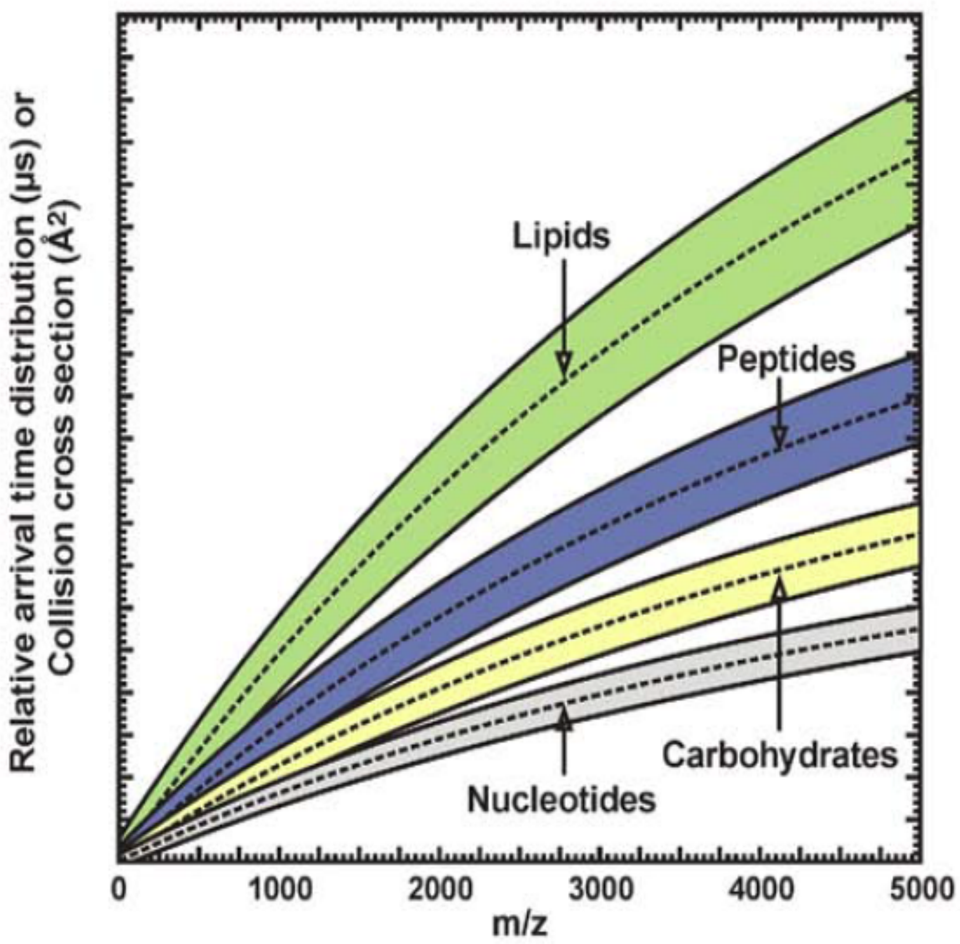
Why would anyone (including yourself) want to use IMS in their studies?

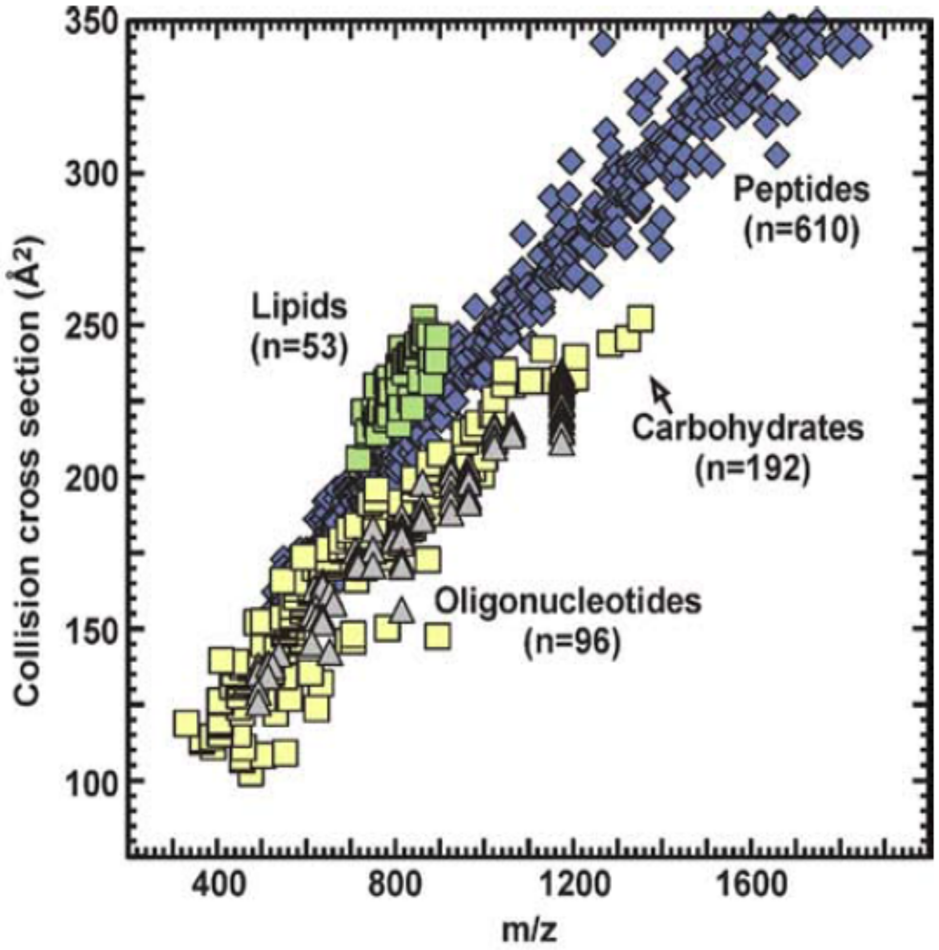
IMS Application – Isomer separation



NW Chem used to model 3-D conformations

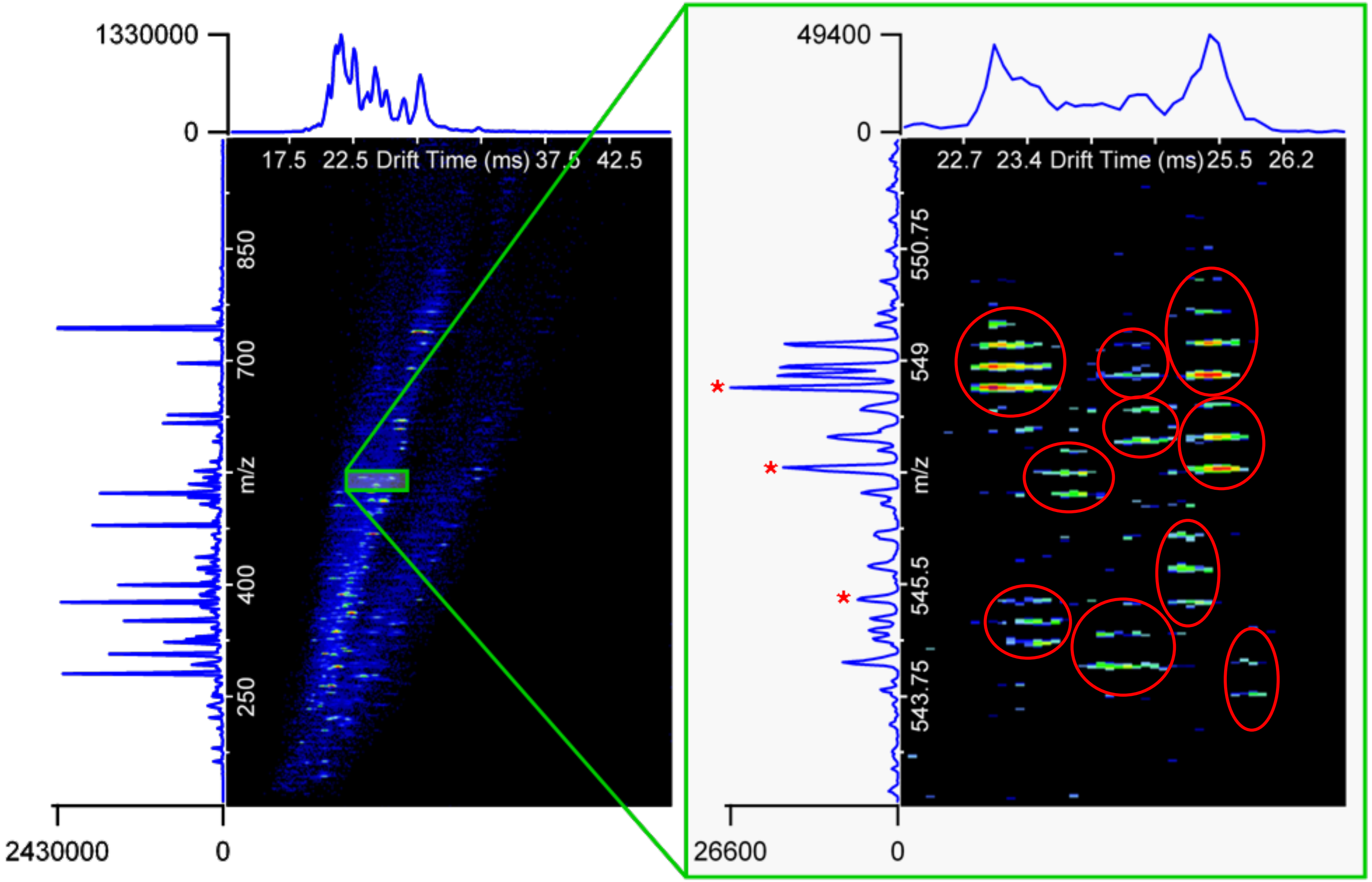
IMS Application – Molecular class separation





J Am Soc Mass Spectrom 2009, 20, 1775–1781.

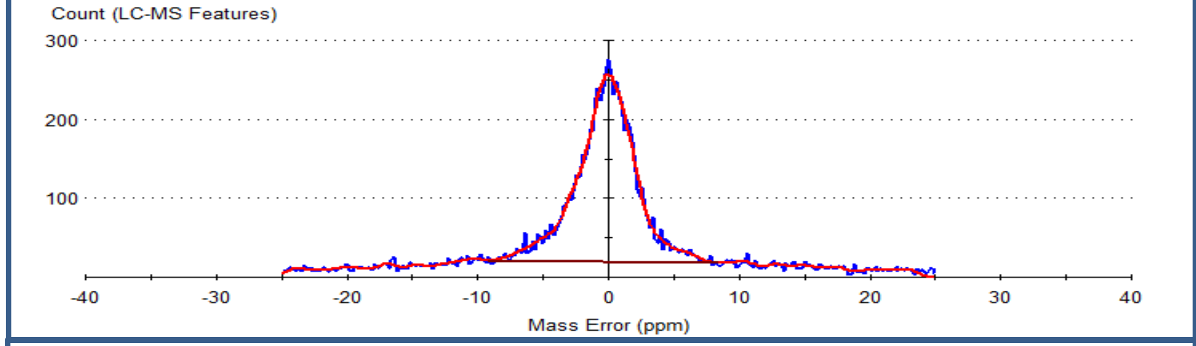
IMS Application – Increased feature detection



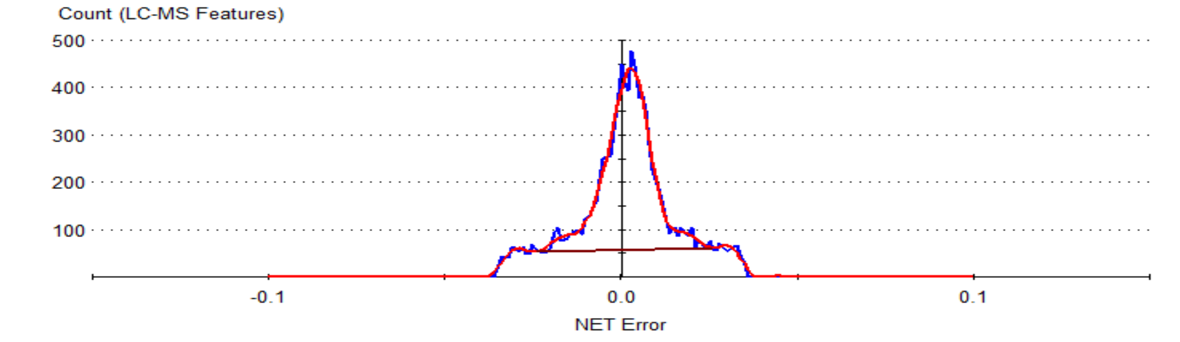
Only 3 features discerned without drift time dimension (*)

IMS Application – Multidimensional library matching

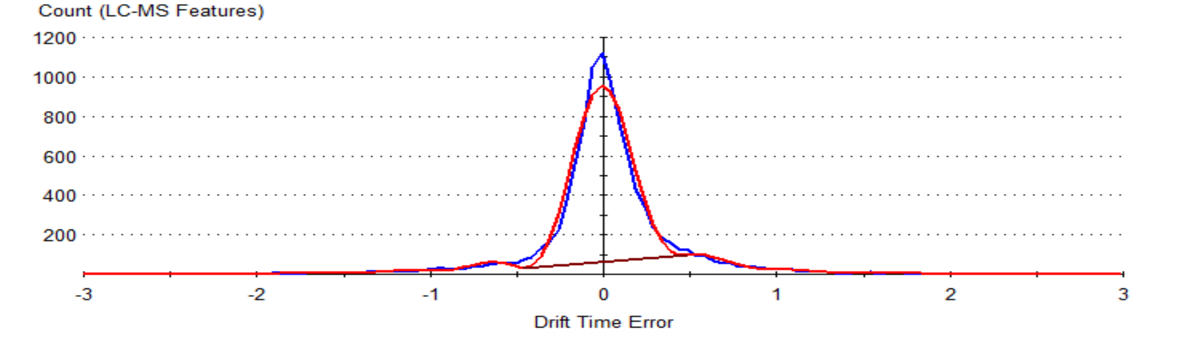
Mass Error



LC Error



Drift Time Error



Human Serum Peptide Analysis

60-min LC-IMS-MS

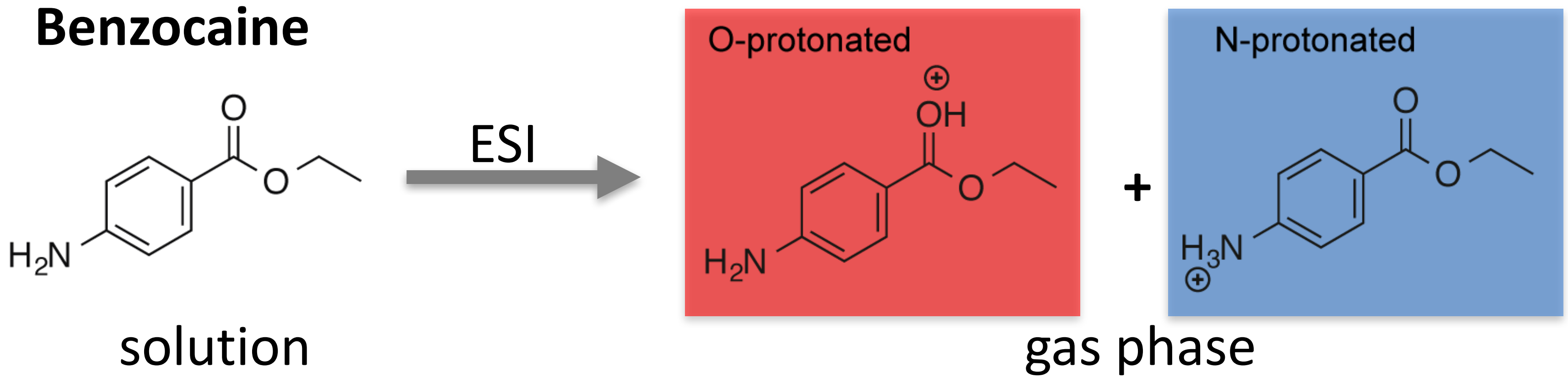
40519 Features with FDR <5%

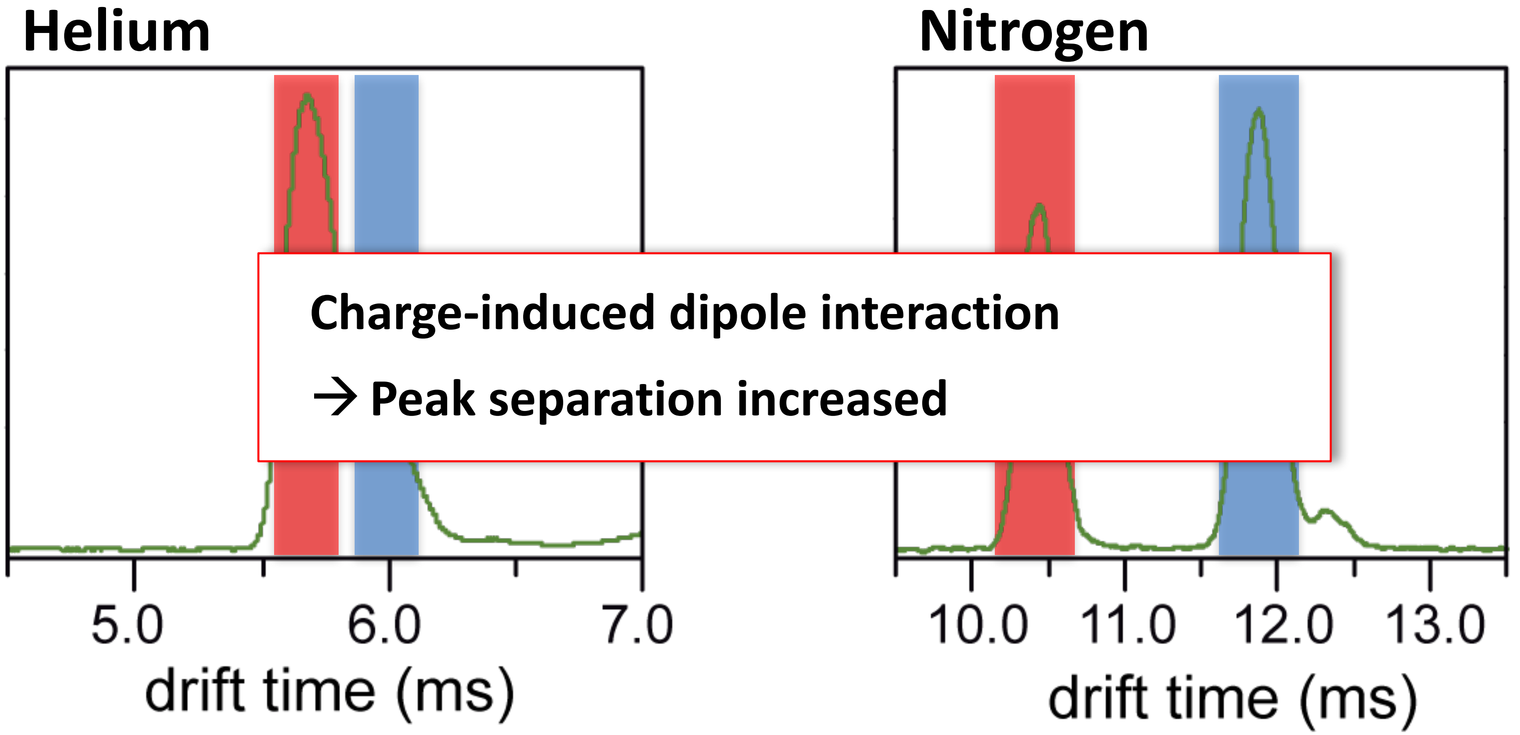
If you only use LC and MS

29007 Features with FDR <5%

Extra dimension adds confidence to LC-IMS-MS Features Matches in a Library

IMS Application – Protomer Separation



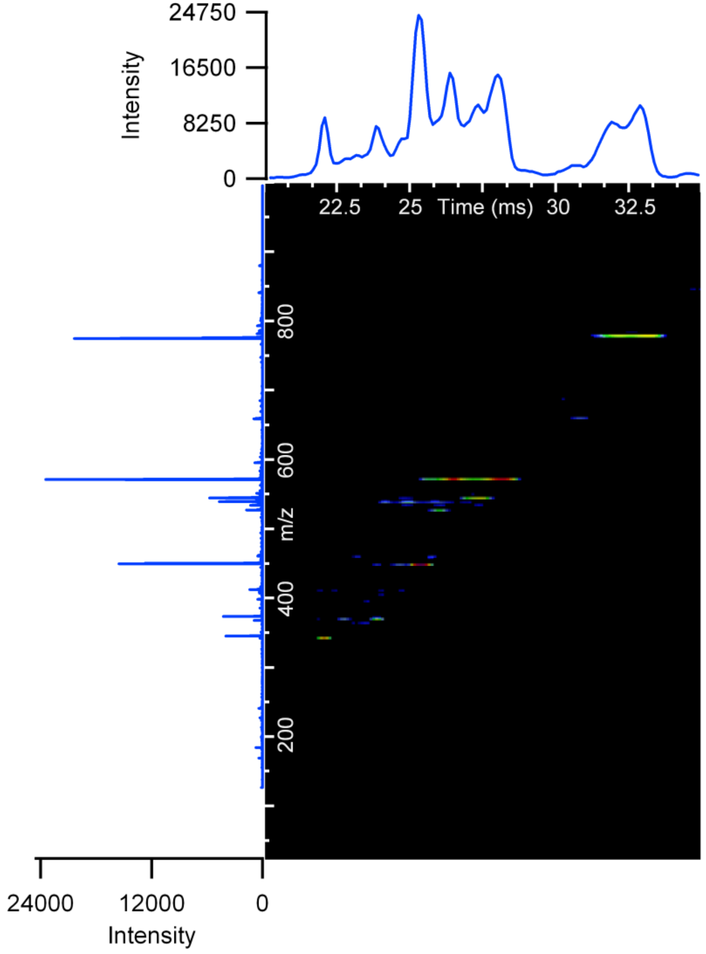


Charge-induced dipole interaction

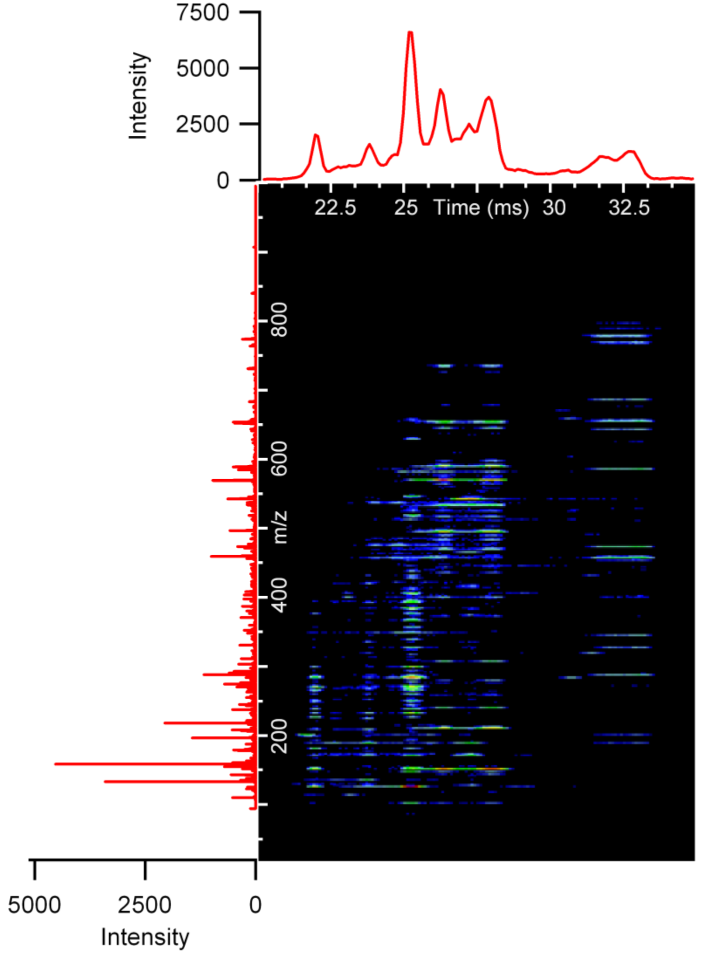
→ Peak separation increased

Warnke, S. et al. *J. Am. Chem. Soc.* 2015, *137*, 4236-4242

IMS Application – Multiplexed fragmentation



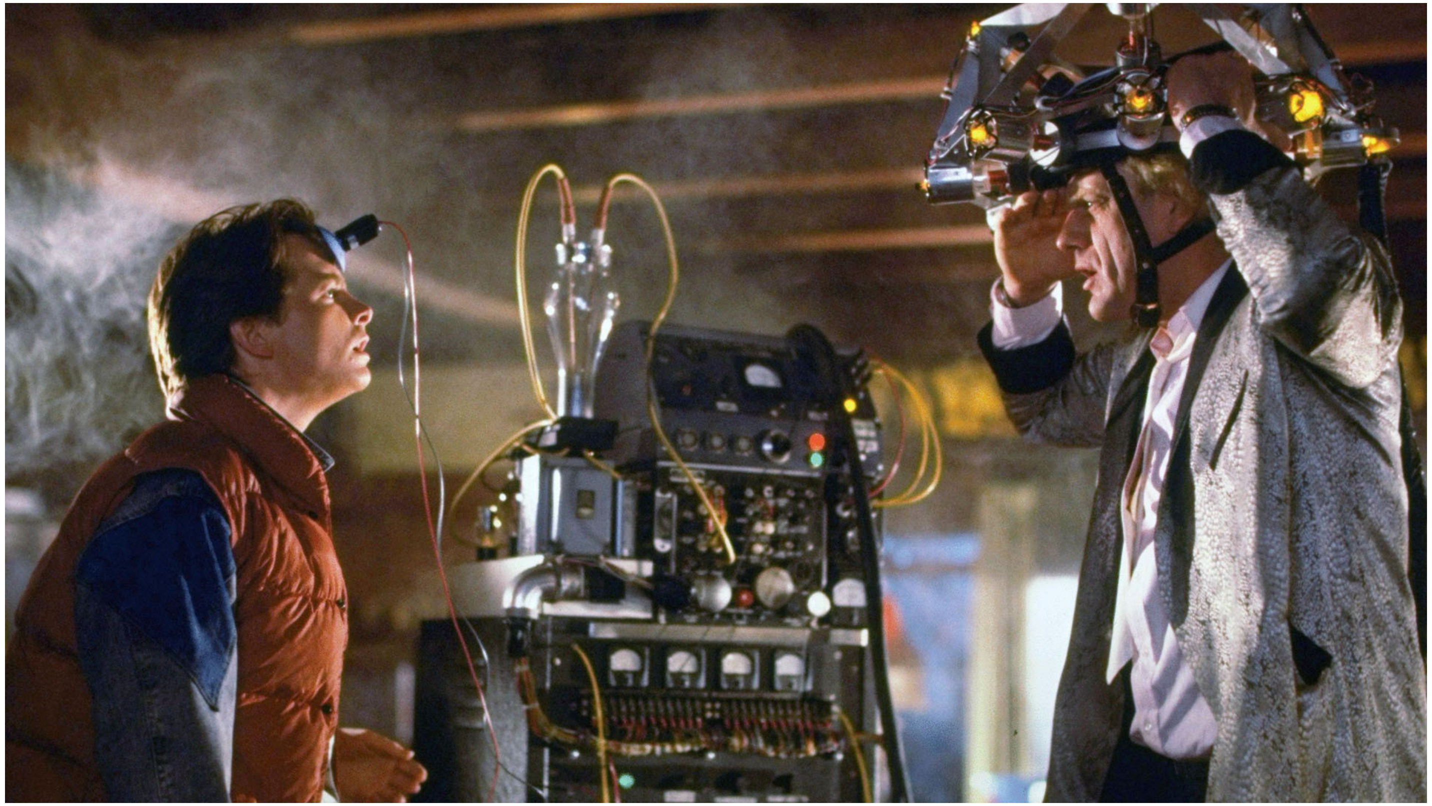
Precursor Spectrum



Fragmentation Spectrum

Fragments have the same drift time as precursors

Interesting Future IMS Applications

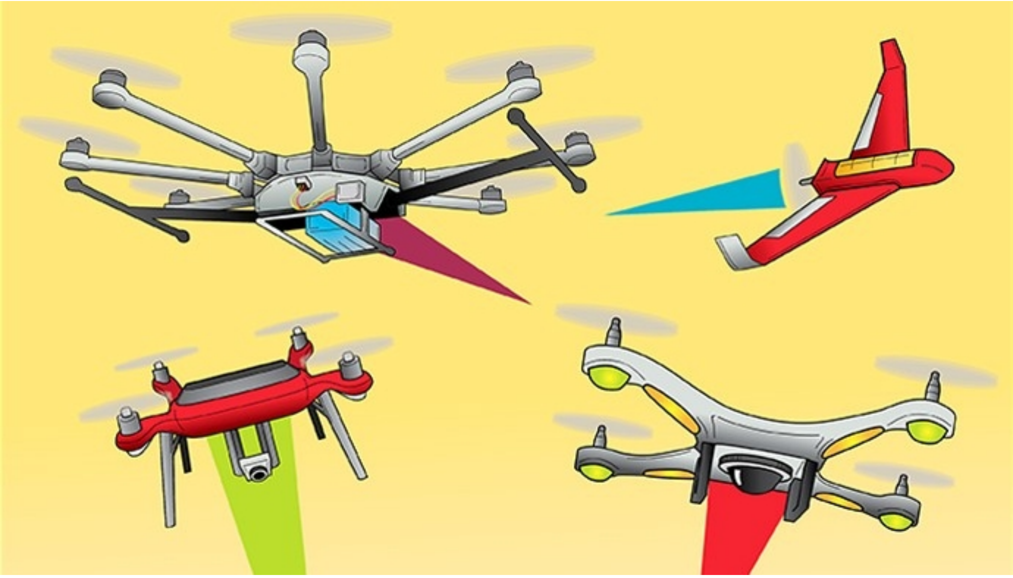


Novel IMS applications – Chemical warfare agents detectors

- Lightweight compact detector (cell phone size)
- Sample the air for traces of nerve gas, blister agents, toxic industrial chemicals, and blood/choking agents
- The unit can check cargo, equipment, personnel or facilities

Novel IMS applications – Drone analyses

- “The U.S. Army’s Edgewood Chemical Biological Center has outfitted drones with ion mobility spectrometers for real-time detection of chemical weapons.”



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Volume 94 Issue 9 | pp. 36-37
Issue Date: February 29, 2016

COVER STORIES: DRONES SWARM TO SCIENCE

Drones detect threats such as chemical weapons, volcanic eruptions

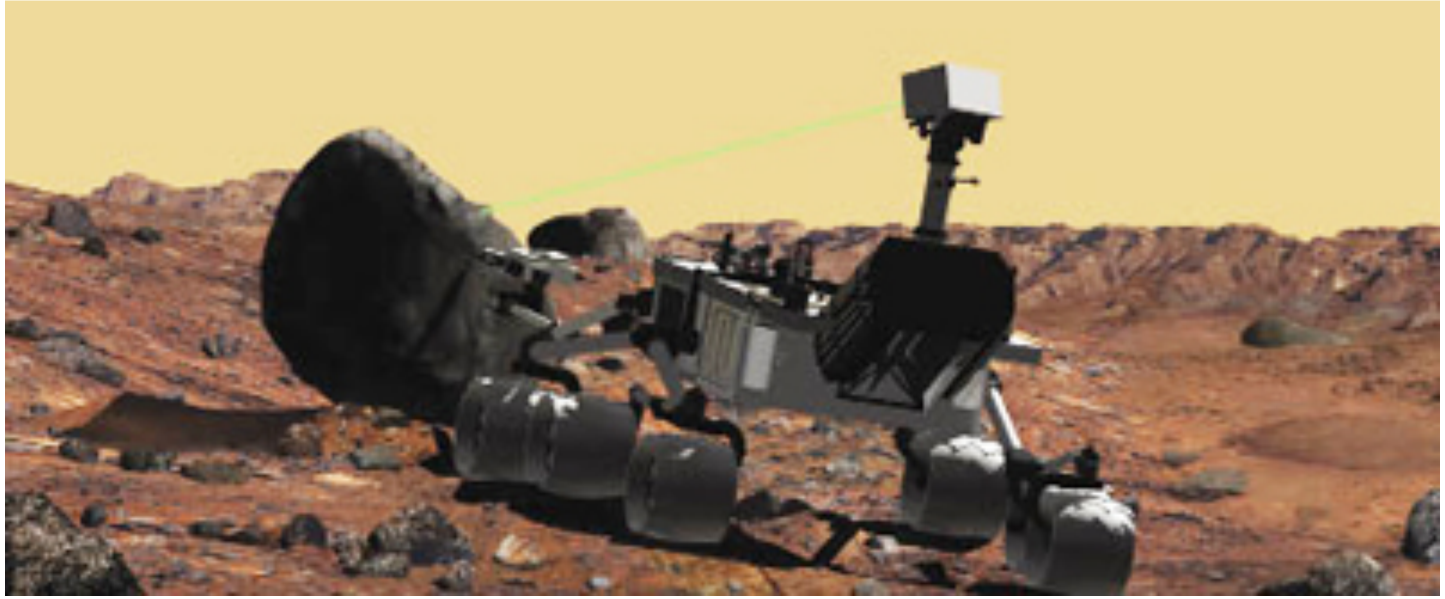
By Sarah Everts and Matt Davenport

Chemical firms survey their plants from the sky

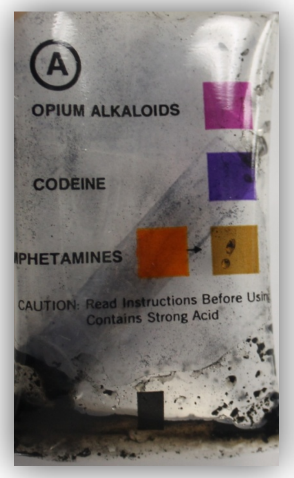
[+]Enlarge

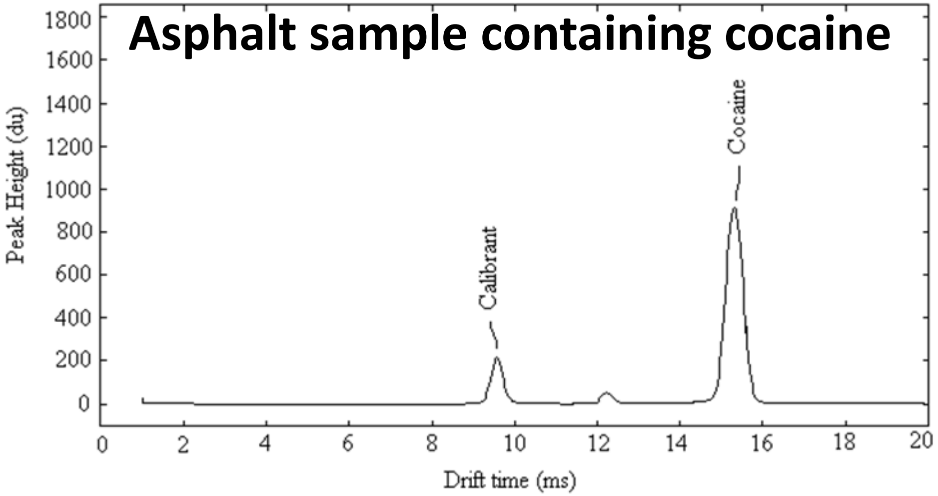
Novel IMS applications – Space travel

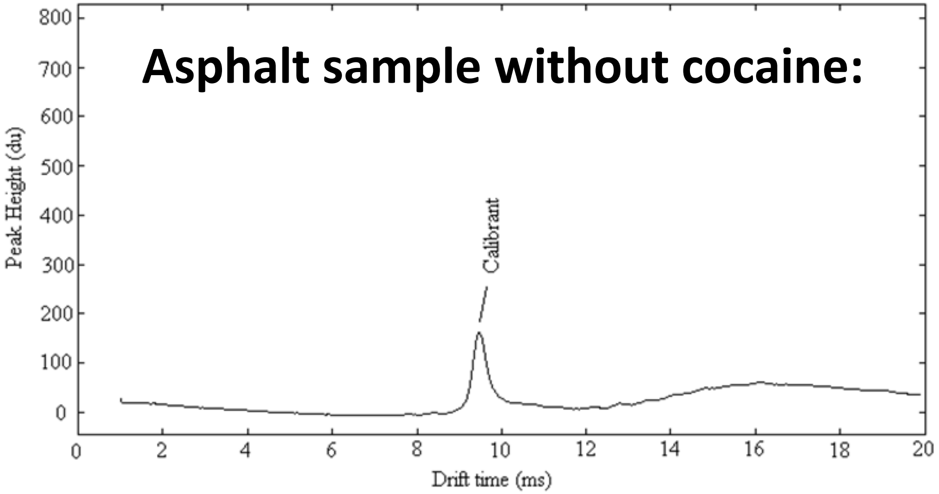
- NASA is working to put IMS devices on future space craft
- IMS is a fast, highly sensitive method for separating and identifying gaseous molecules
- Need consistent, high-level operation in harsh conditions without maintenance



Novel IMS applications – Drug analyses



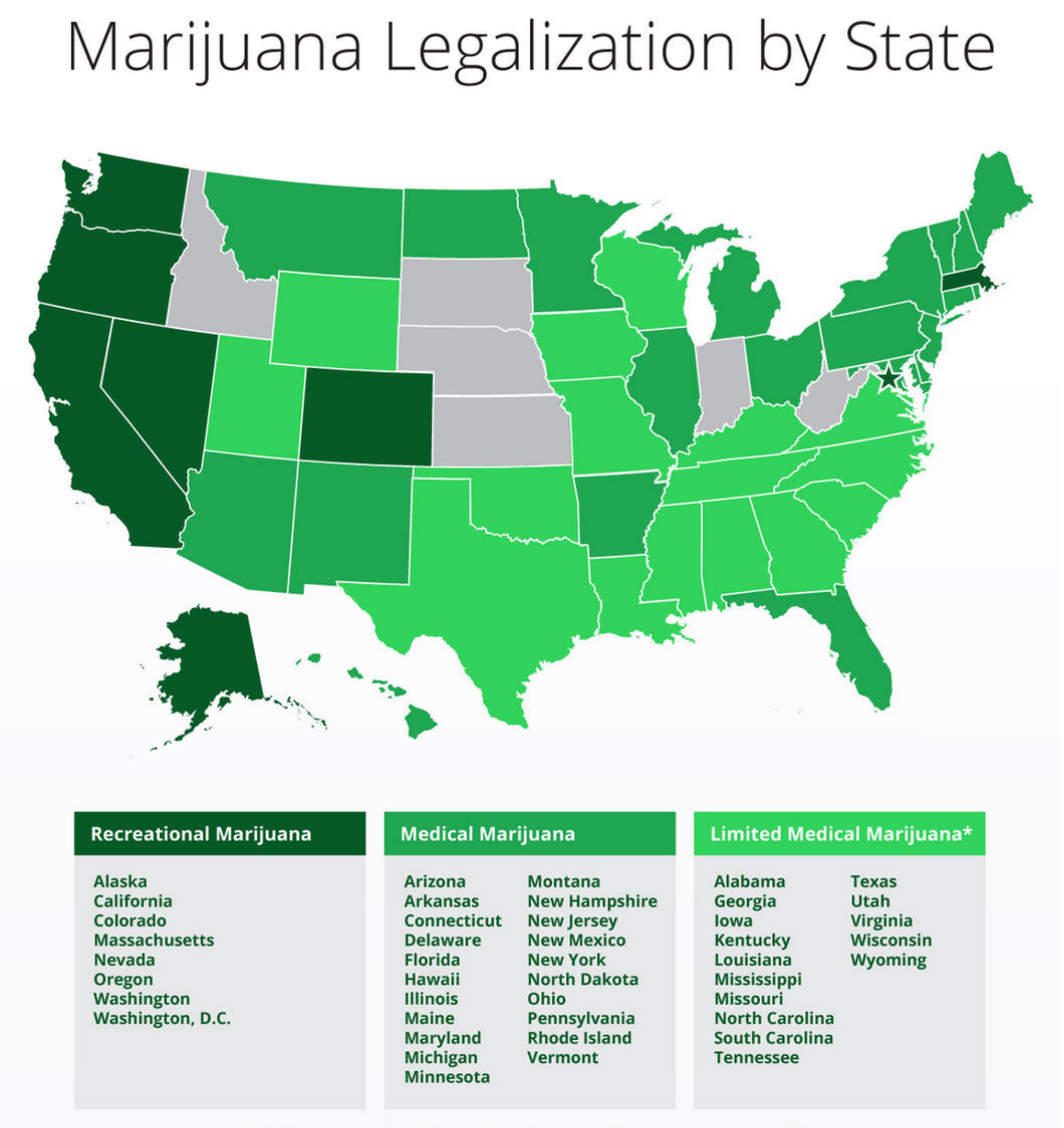




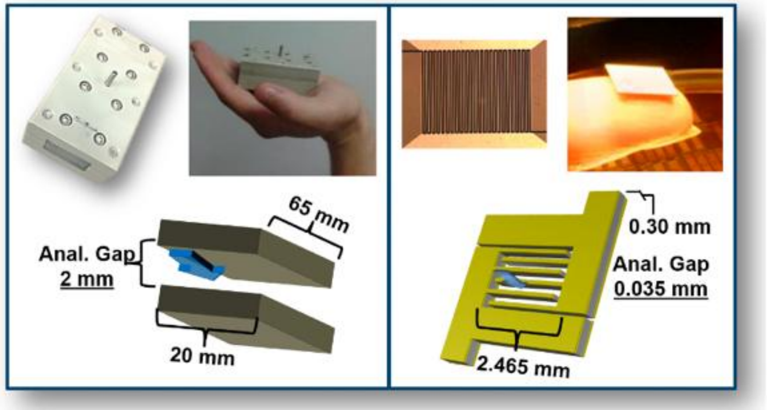
M. J. Binette, P. Pilon, “Detecting black cocaine using various presumptive drug tests”, Microgram 2013, 10, 8 – 11.

Slide courtesy of Professor Brian Clowers

Novel IMS applications – Marijuana detection

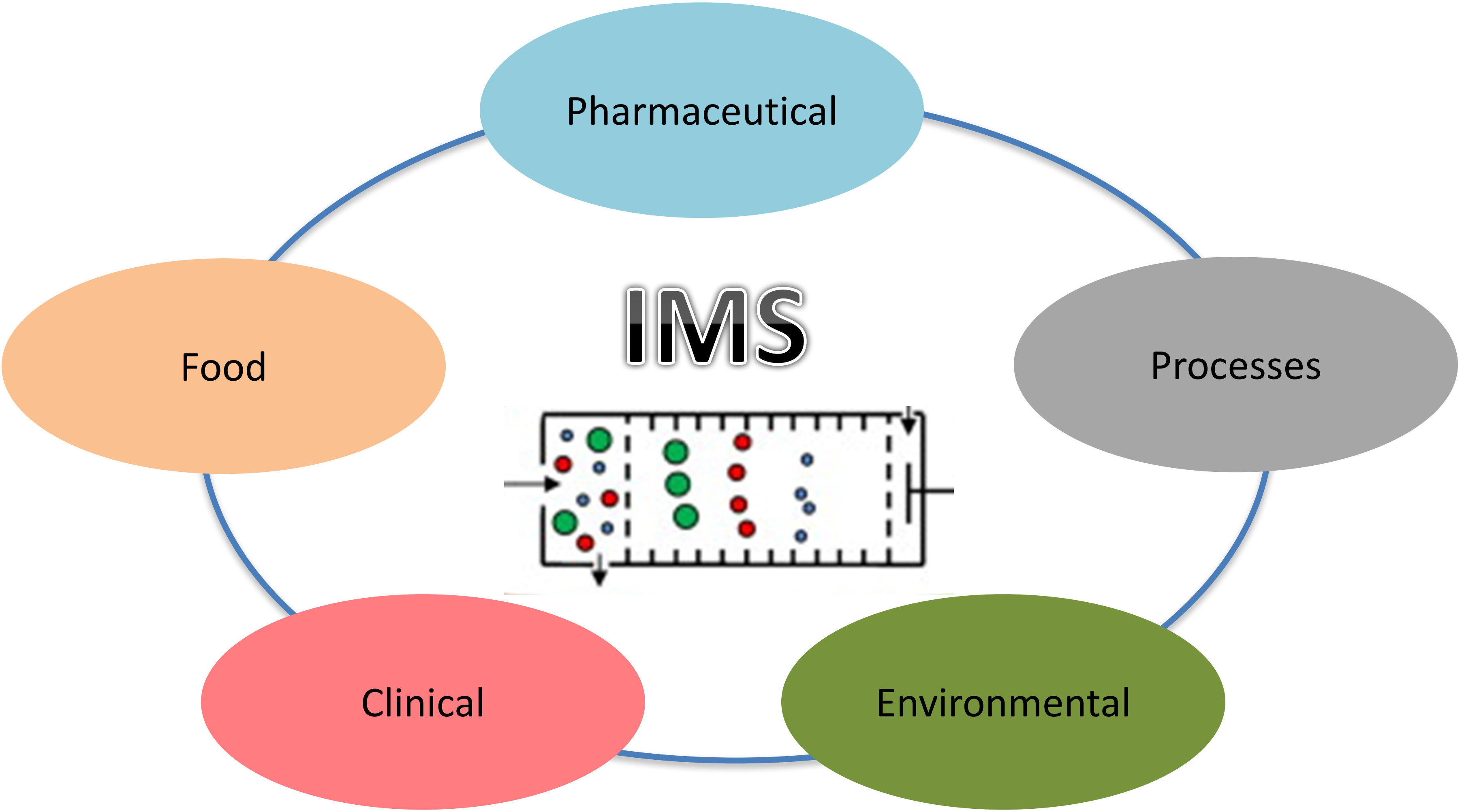


THC Detection



FAIMS Receptors

Novel IMS applications – Broad application space



Summary

- Define ion mobility spectrometry (IMS)
- Differences between the diverse IMS methods
  (i.e. DTIMS, TWIMS, FAIMS, DMA, TIMS, etc.)
- Benefits of using IMS
- Current and future IMS applications

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