Towards total ion utilization: Electrospray ionization in a sub-ambient pressure environment for high sensitivity mass spectrometry

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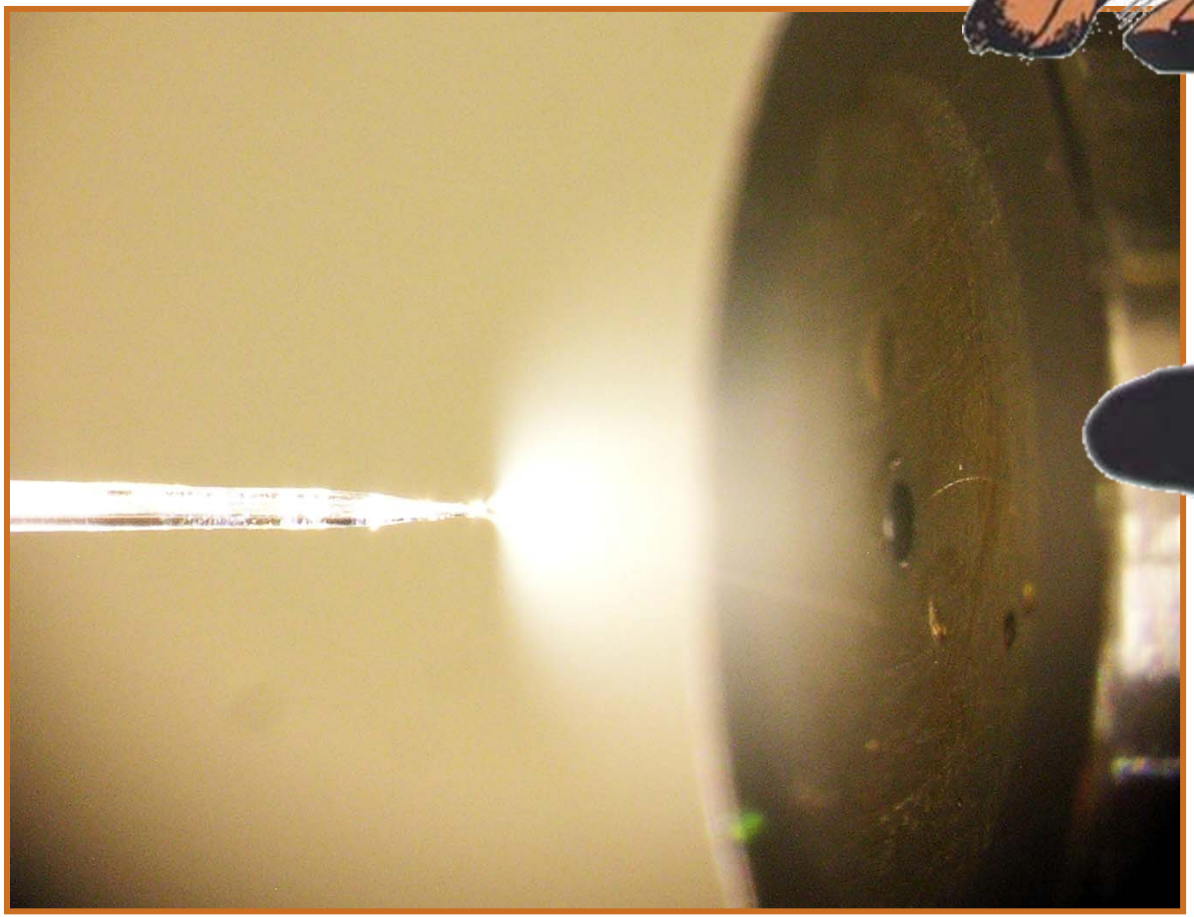
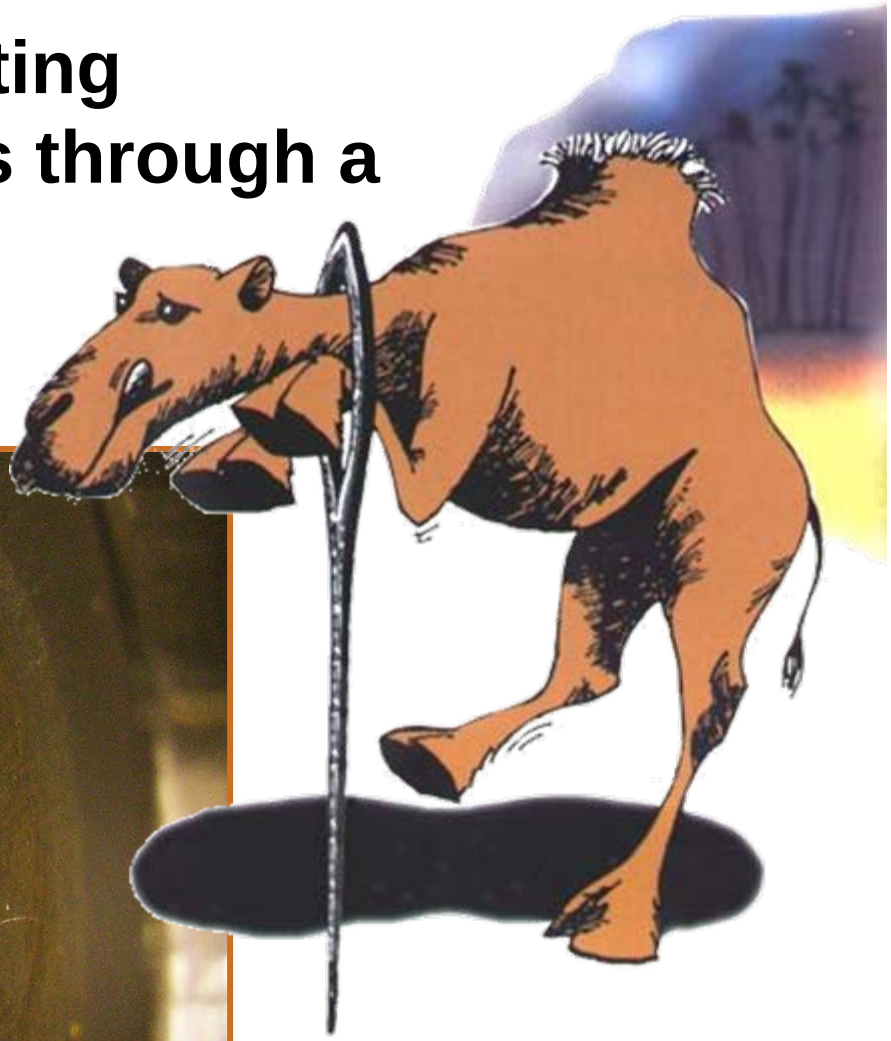
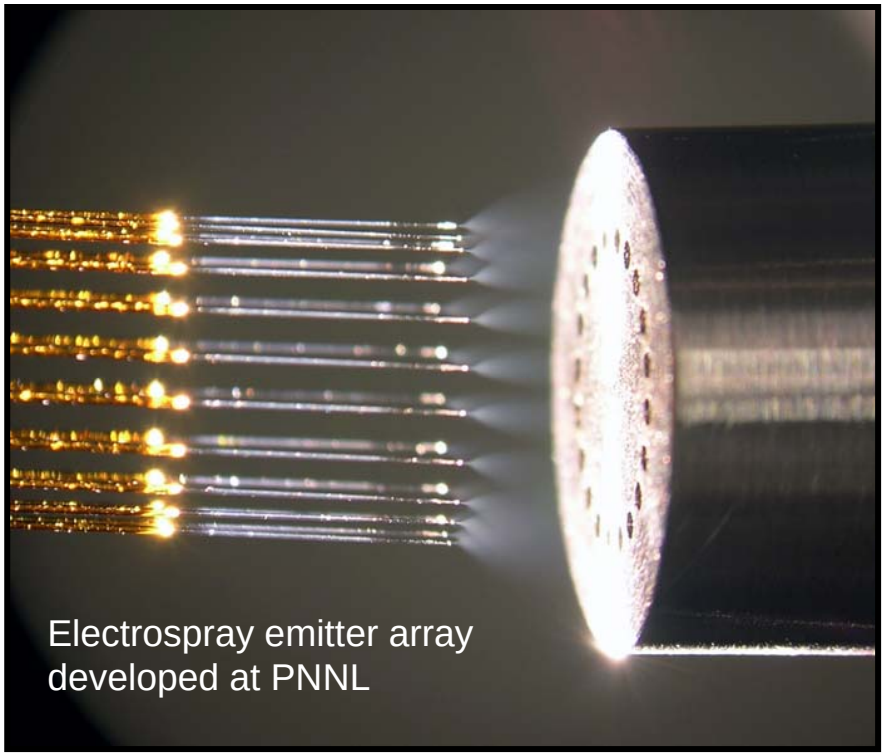
The challenge of transmitting electrospray ions/droplets through a capillary MS inlet





Large ion losses associated with the MS inlet

- The MS inlet is a barrier to total ion utilization
- Typical LC-MS inlet *charge* transmission efficiencies are presently only ~0.1 – 10%*



* Page, J.S. et al. *J. Am. Soc. Mass Spectrom.* **2007**, *18*, 1582.
Marginean, I. et al. *Anal. Chem.* **2008**, *80*, 6573.

Operation of electrosprays inside the ESI-MS Interface?

- Previous work with electrosprays < mTorr

  - primarily electrohydrodynamic ionization*

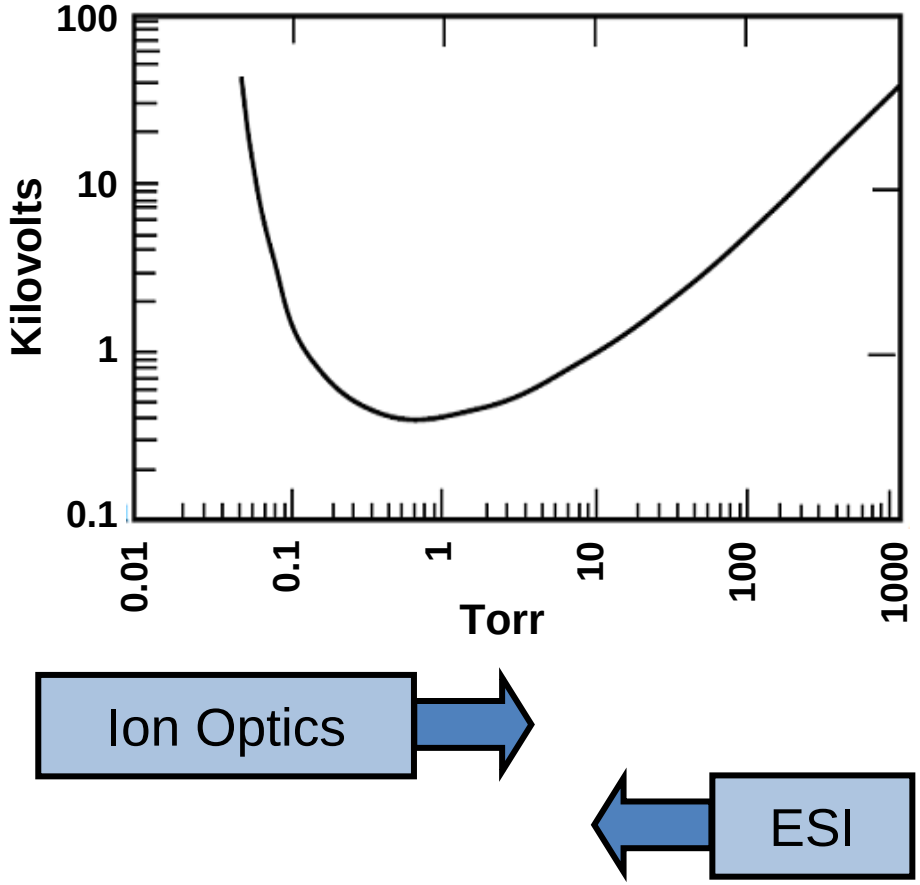
  - used glycerol, liquid metals, ionic liquids (low vapor pressure, *very* low flow rates)

- Present focus using LC compatible solvents (i.e. high vapor pressure)

- Challenges: Solvent freezing and boiling, in addition to electrical breakdown

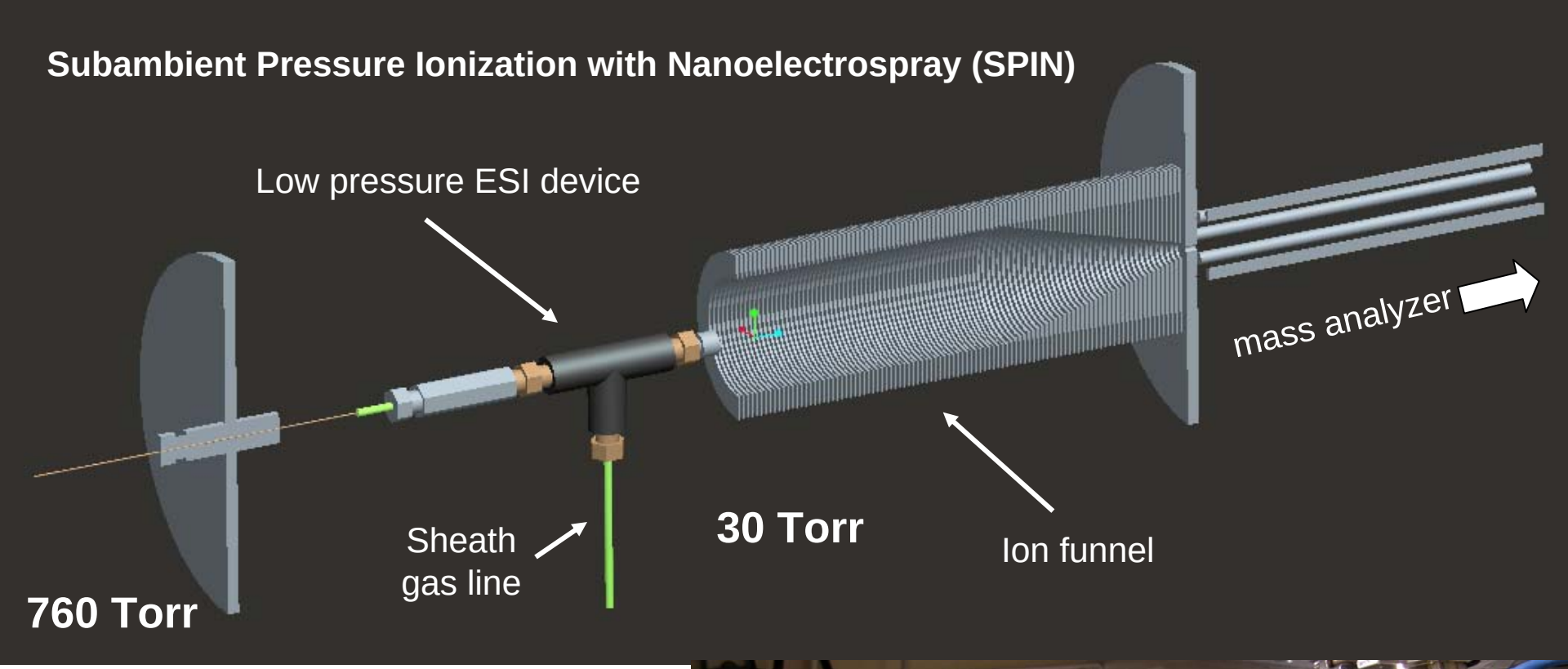
- *Requires electrospray at pressures both high enough to prohibit freezing, etc. and low enough to allow efficient transmission*

Breakdown voltage versus pressure for a 1 cm gap



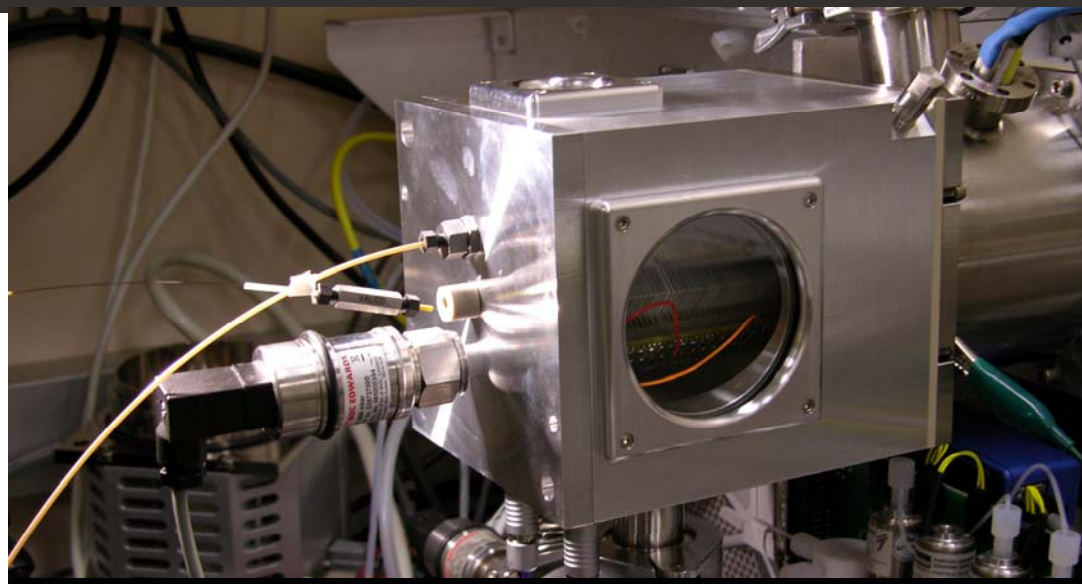
* Cook, K. D. *Mass Spectrom. Rev.* **1986**, *5*, 467.

Subambient Pressure Ionization with Nanoelectrospray (SPIN)



Low pressure ESI device:
Enables ESI at reduced pressures at the entrance to an RF ion guide

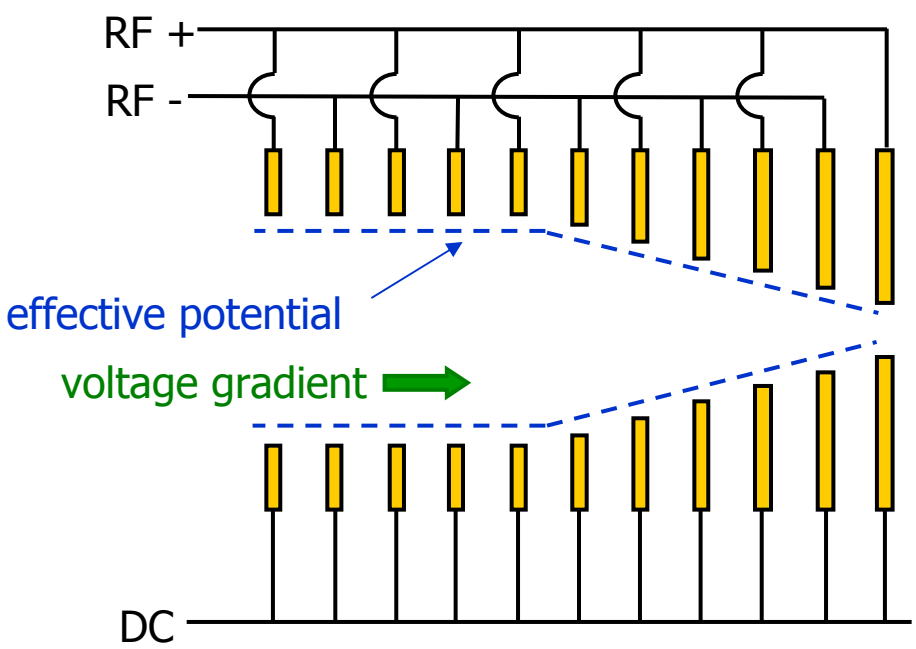
Ion funnel: Provides effective ion transmission and electrospray droplet desolvation at 30 Torr

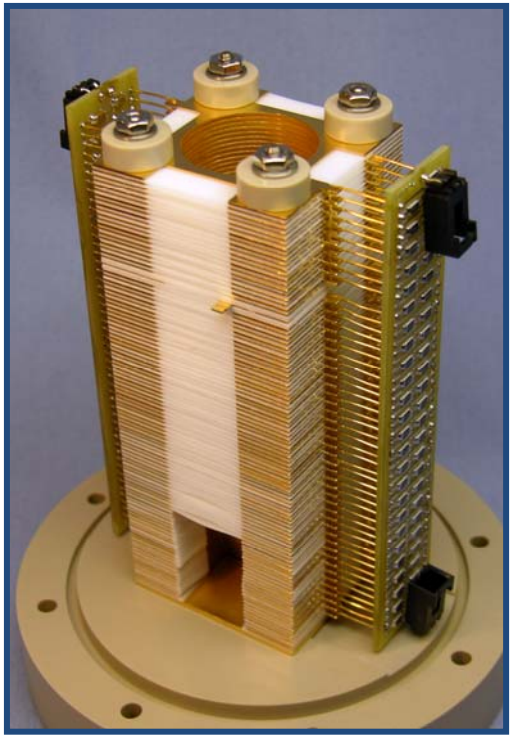


SPIN source on an Agilent single quad mass spectrometer

Electrodynamic Ion Funnel

- Stacked-ring ion guide tapered to the i.d. of the conductance limiting orifice
- Starting i.d. = 25 mm; ending i.d.= 2 mm
- RF range = 0.5 – 2.0 MHz; 40 – 200 Vp-p
- Operating pressure range = 1 – 30 Torr

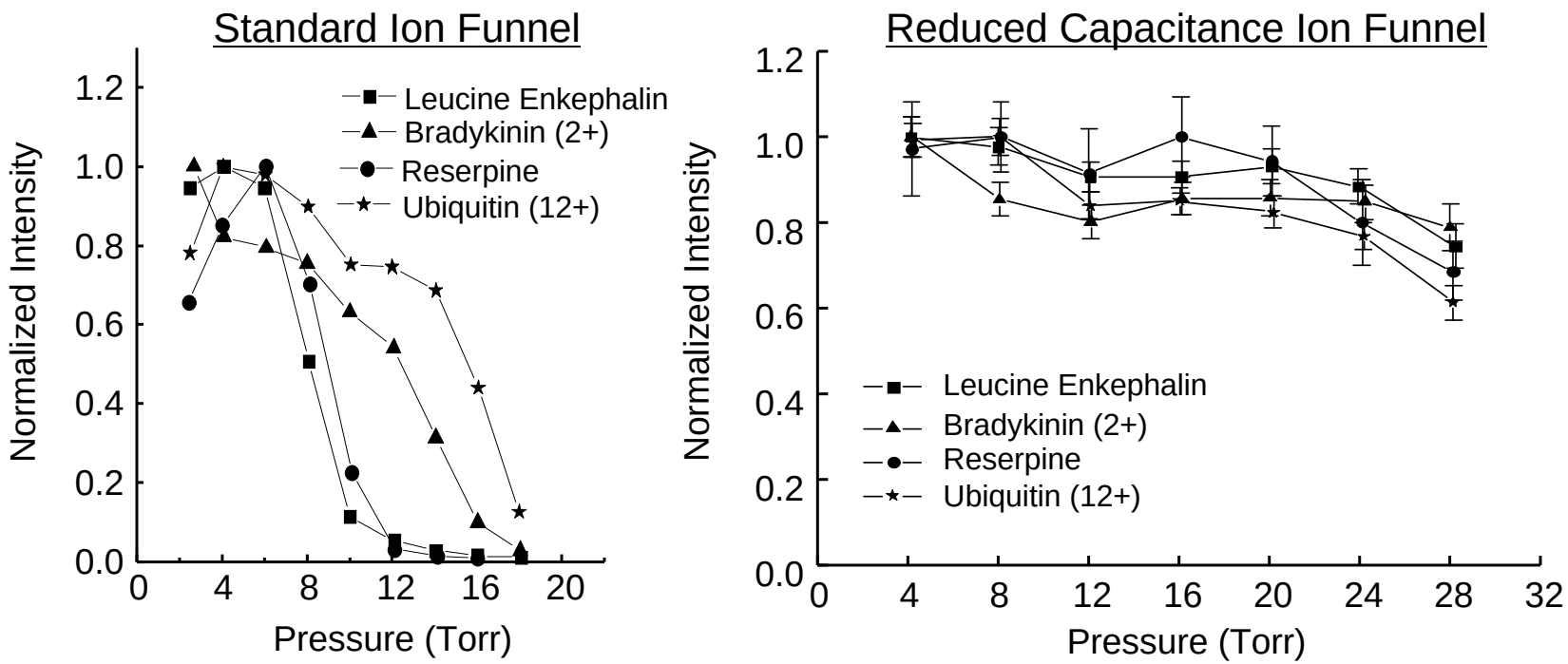




Electrodynamic Ion Funnel

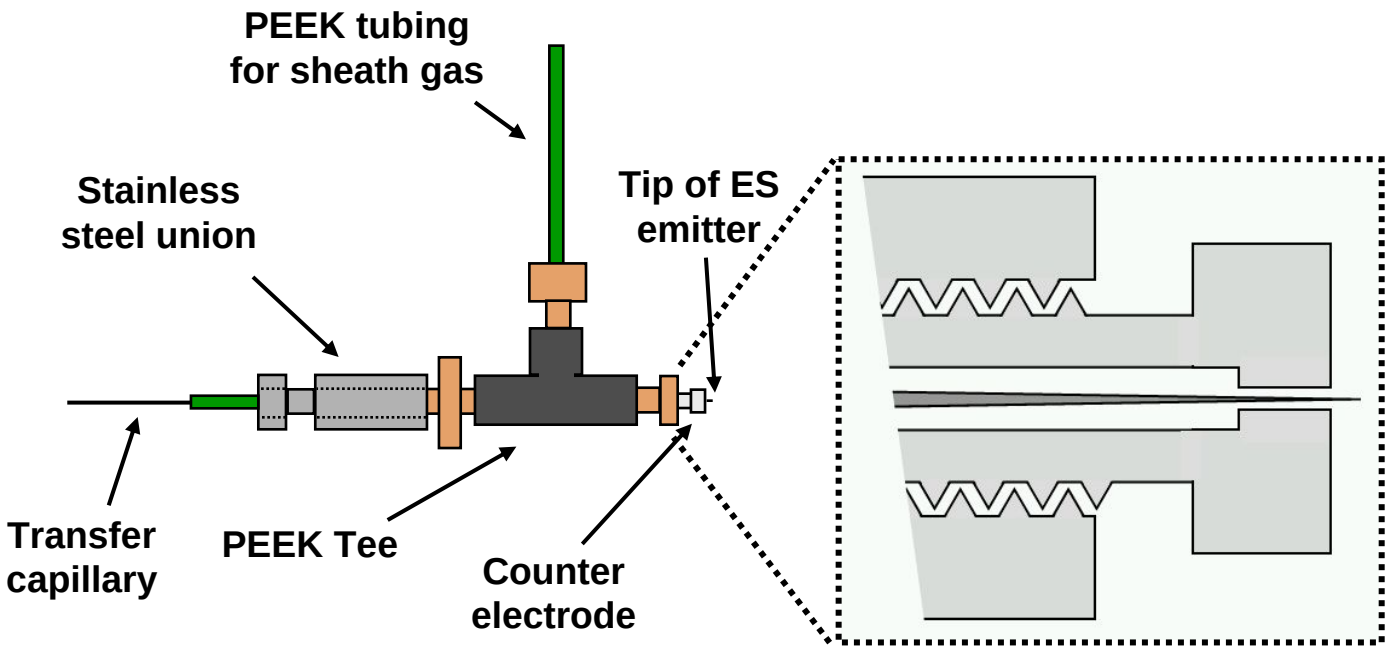
- Stacked-ring ion guide tapered to the i.d. of the conductance limiting orifice
- Starting i.d. = 25 mm; ending i.d.= 2 mm
- RF range = 0.5 – 2.0 MHz; 40 – 300 Vp-p
- Operating pressure range = 1 – 30 Torr

Normalized intensity versus ion funnel chamber pressure



Ibrahim et al. *J. Am. Soc. Mass Spectrom.* **2006**, 17, 1299.

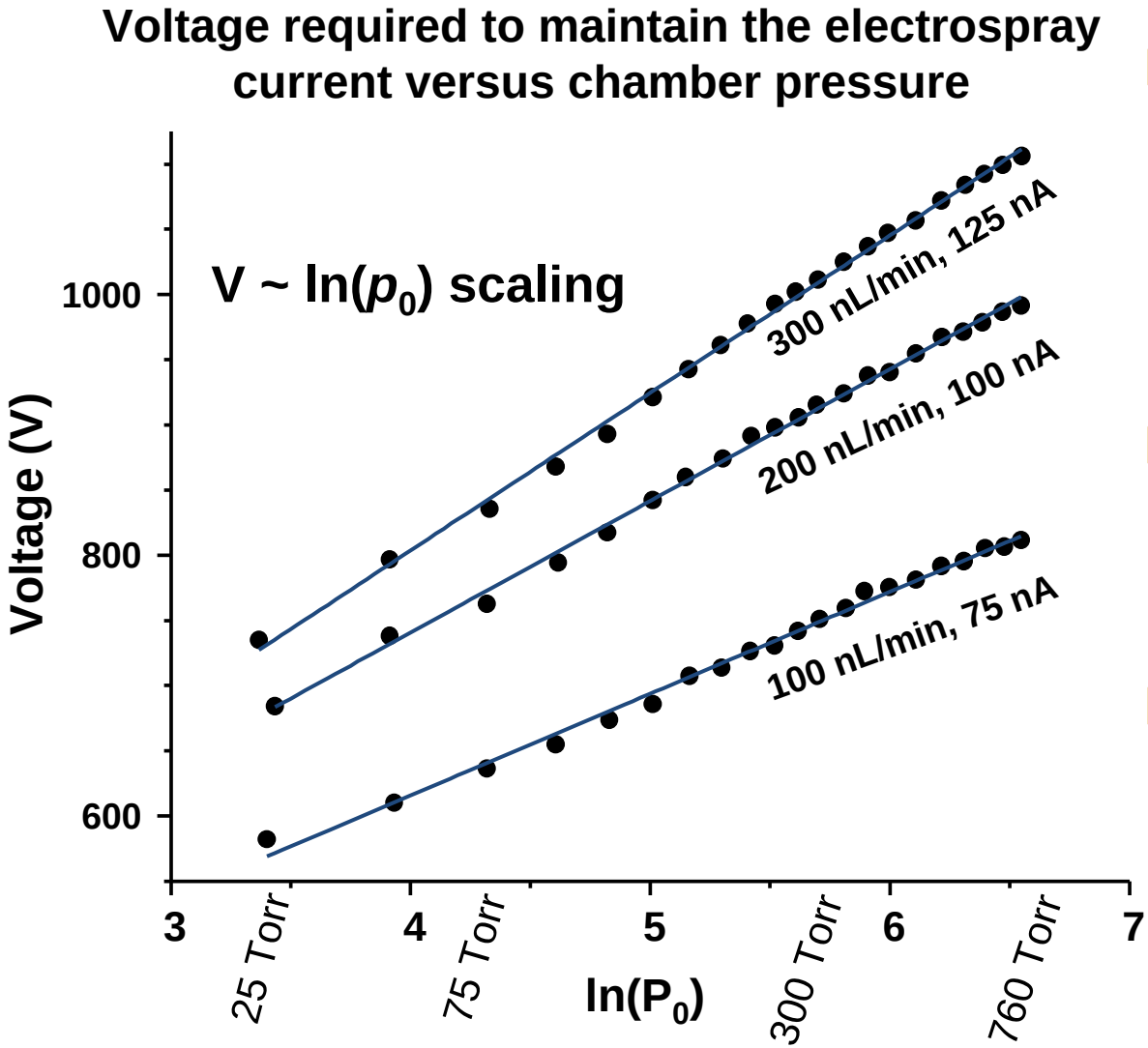
Low Pressure ESI Device



- Enables ESI at reduced pressures at the entrance of the ion funnel.
- Recessed counter electrode.
- Ability to deliver a sheath gas.
- Houses a chemically etched electrospray emitter.

Page, J. S. et al. *Anal. Chem.* **2008**, 80, 1800.

Characterization of ESI at reduces pressures using LC compatible solvents



- Voltage required to maintain the electrospray current decreases at lower pressures
- Difficult to maintain electrosprays at < 25 Torr
- Liquid vapor pressure limits the useful pressure domain

Marginean, I. et al. *Appl. Phys. Lett*. submitted

Comparing a standard capillary inlet to the SPIN source using a MS tuning solution

<u>Capillary inlet ESI-MS interface</u>

7.6 cm, 480 µm i.d., heated inlet

Ion funnel interface

Agilent tune mix

300 nL/min

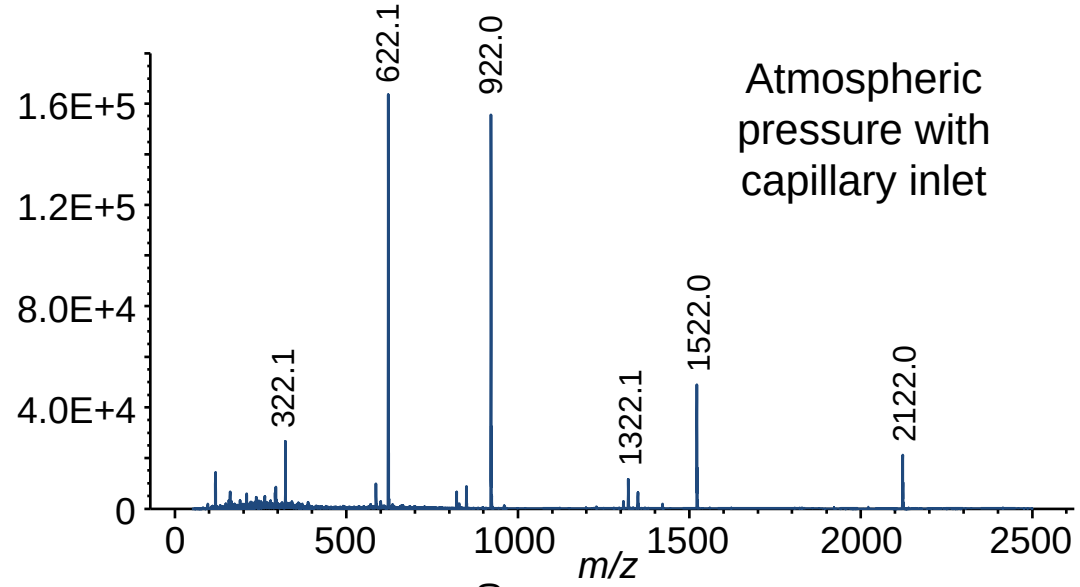
<u>SPIN-MS interface</u>

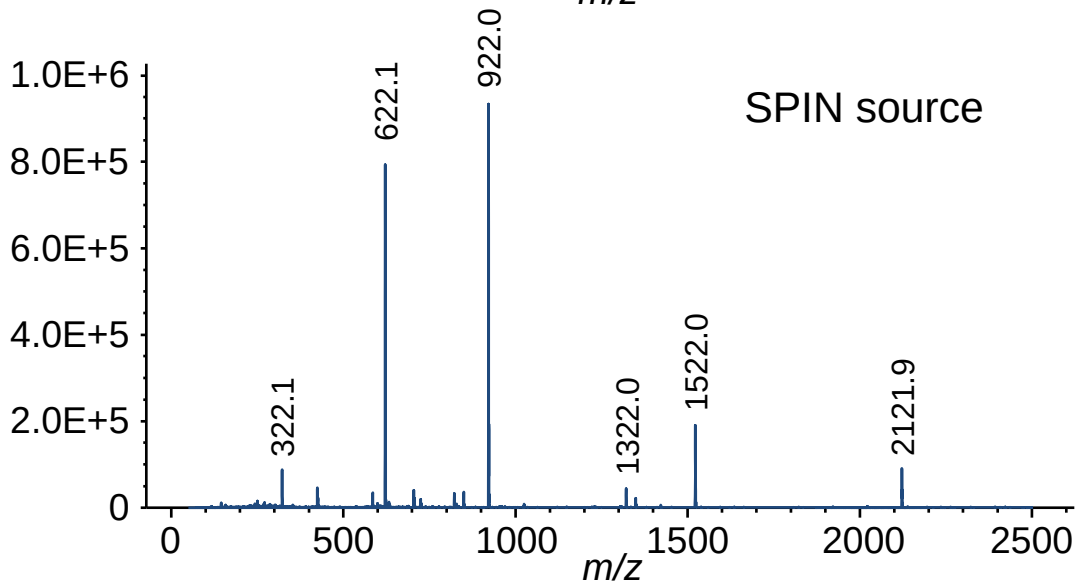
30 Torr ESI

Agilent tune mix

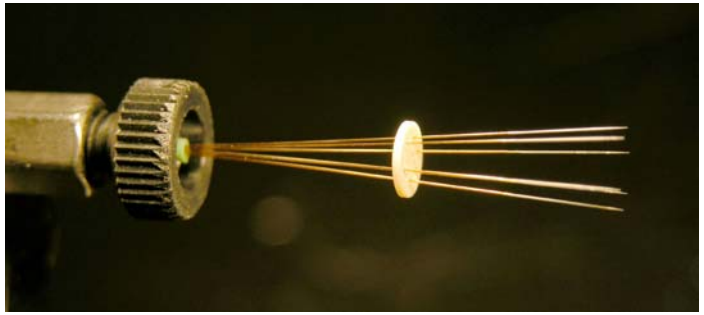
300 nL/min

- Good sensitivity
- Similar profiles
- ‘Cleaner’ baseline



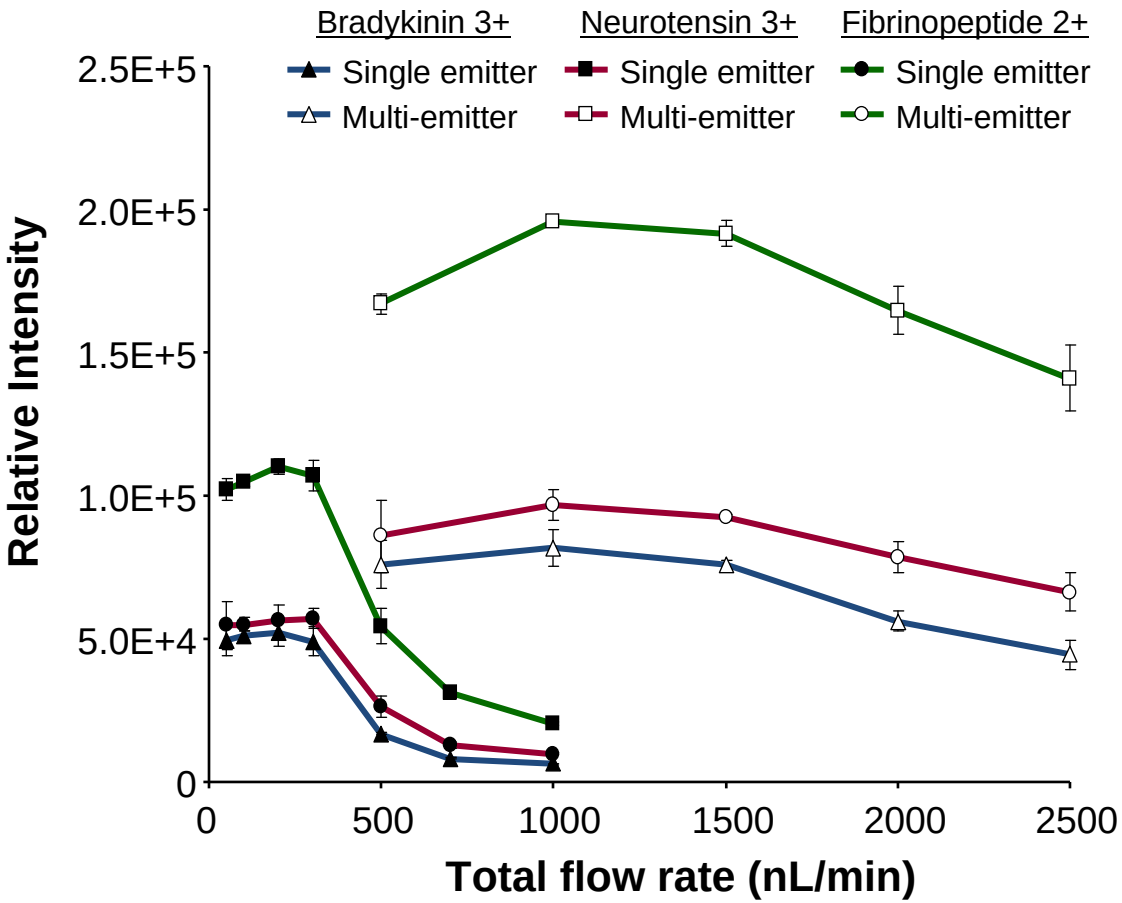


Increasing the SPIN source flow rate range using electrospray emitter arrays



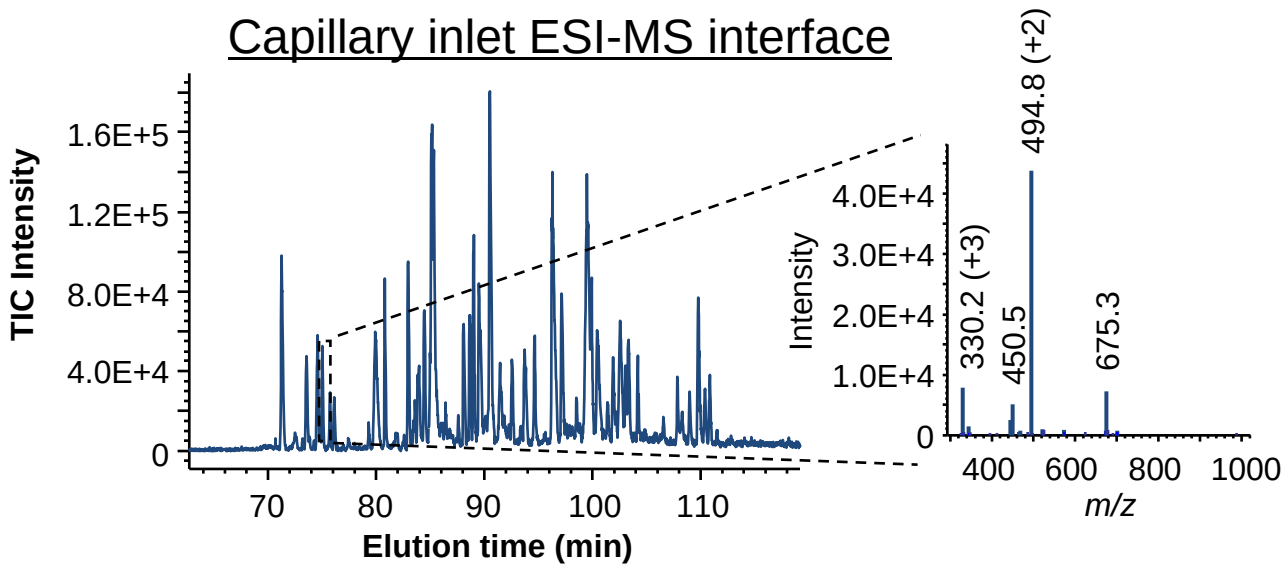
- 1 µM peptide solution in 50:50 MeOH/H_2O + 1% acetic acid
- Higher flow rates with the single emitter decrease peak intensity due to incomplete desolvation
- Lower flow rates = smaller, more highly charged droplets which are more easily desolvated
- Use of emitter arrays provide benefits of low flow electrospray with higher and more robust LC flow rates

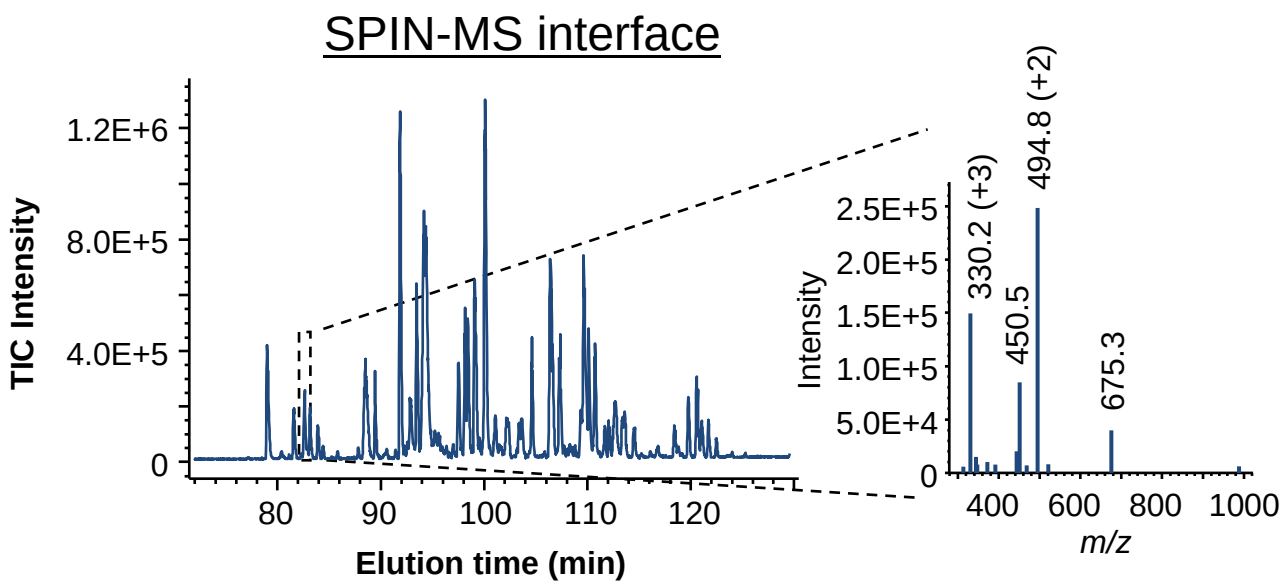
MS intensity versus flow rate for a single emitter and 6-emitter array with the SPIN source



Implementation with HPLC/MS

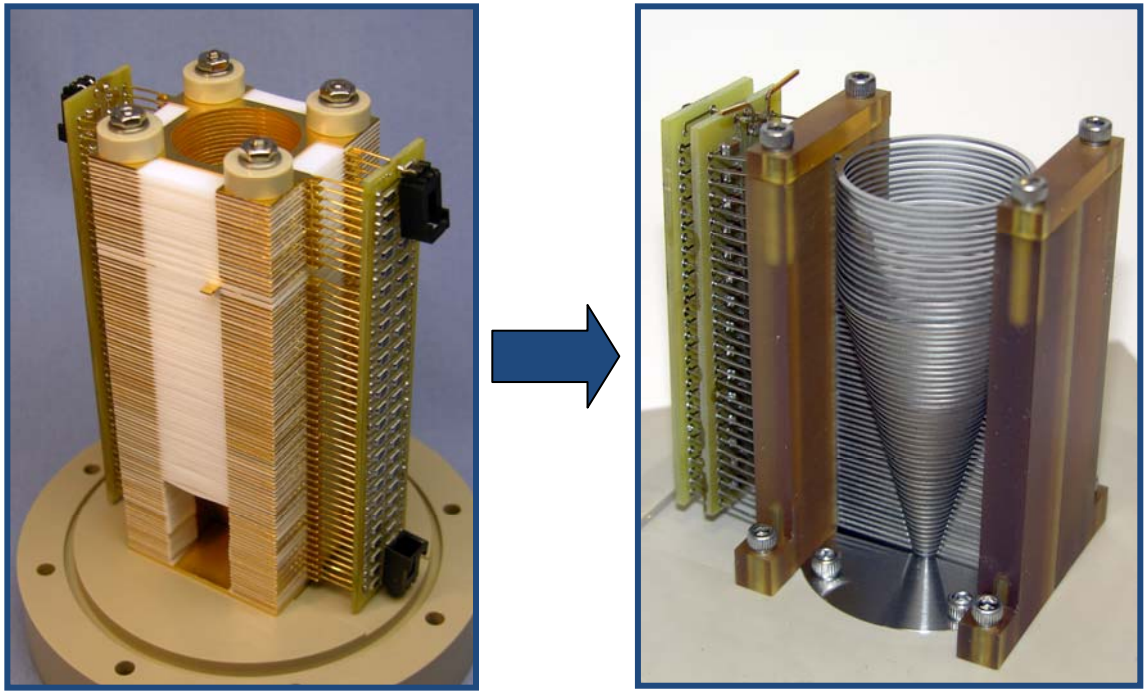
- 0.5 µg of a BSA tryptic digest loaded onto a 75-µm-i.d. packed column (3-µm porous C18 particles, flow rate of 300 nL/min)
- Standard ESI used a 7.6-cm-long, 480-µm-i.d., heated capillary
- Both sources used 30 Torr and 1.7 Torr tandem ion funnels
- SPIN source provided increased sensitivity, especially for higher charge state peptides





Increasing the operating pressure of the ion funnel

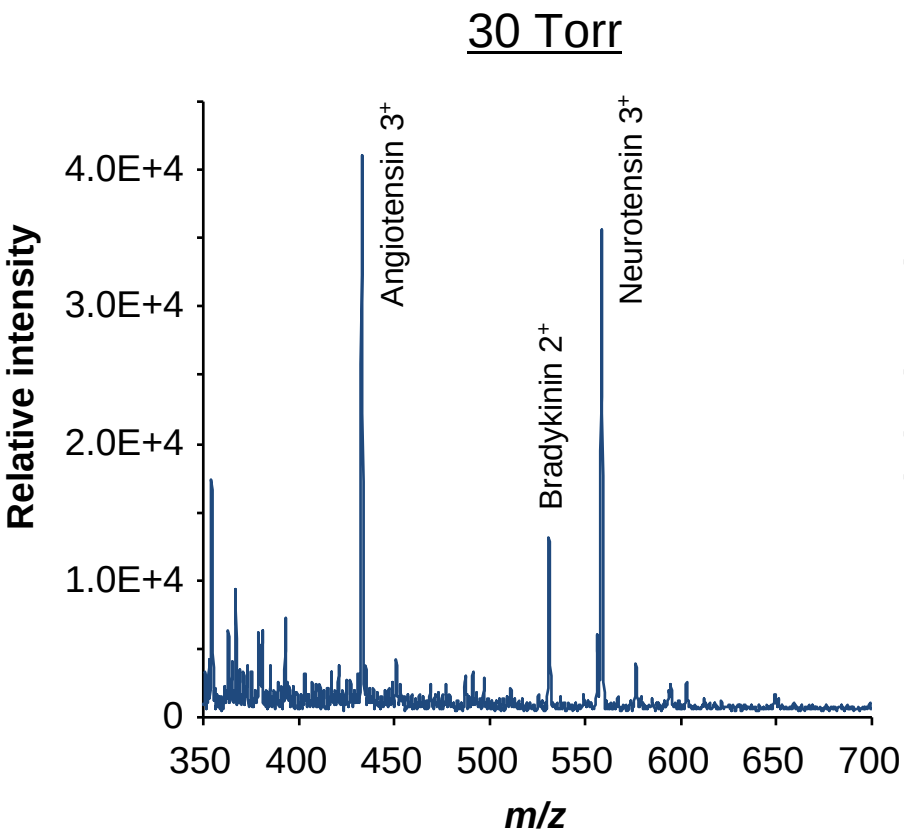
- Higher operating pressures require greater RF frequencies and voltages
- Effective potential scales inversely with the square of the frequency
- Lower ion funnel electrical capacitance eases RF supply power requirements

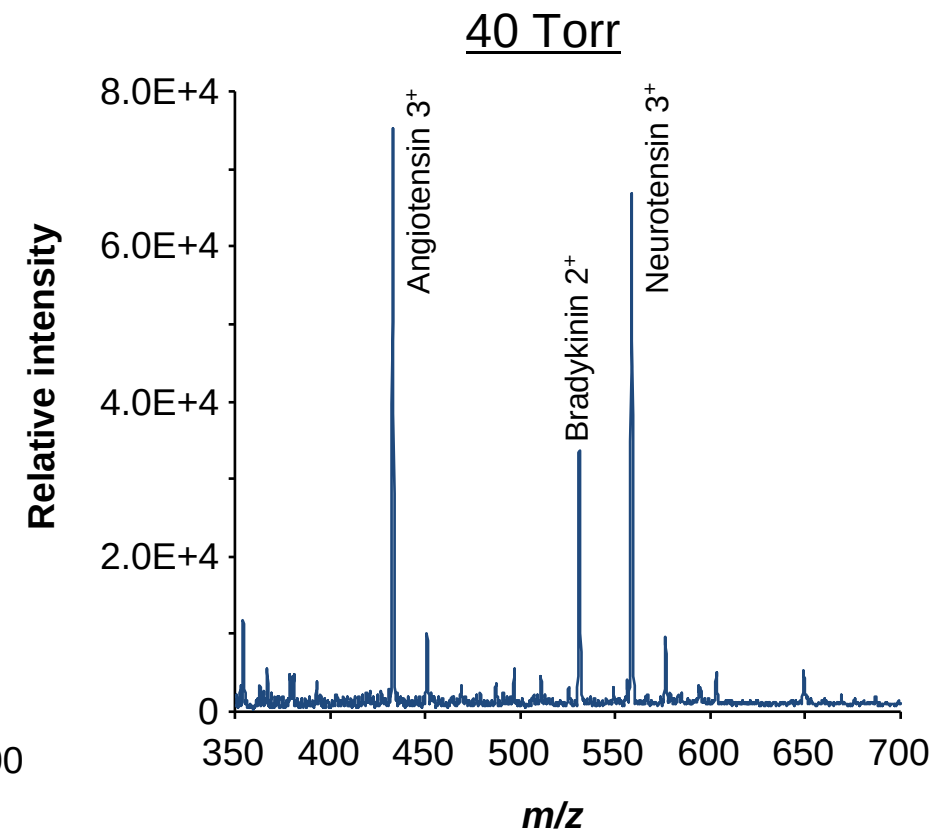


New ion funnel with reduced electrical capacitance

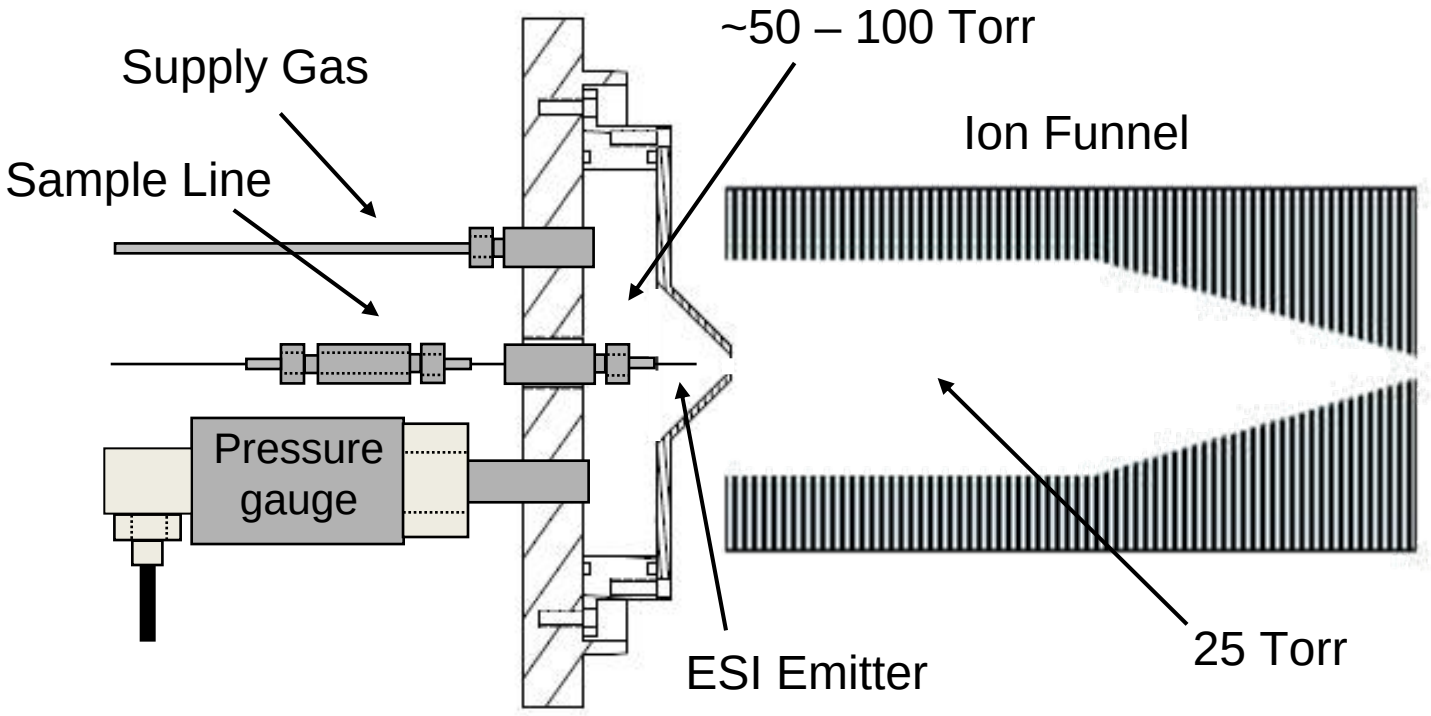
Increasing the operating pressure of the ion funnel

- Effective ion focusing to 45 Torr
- Higher pressure improves desolvation





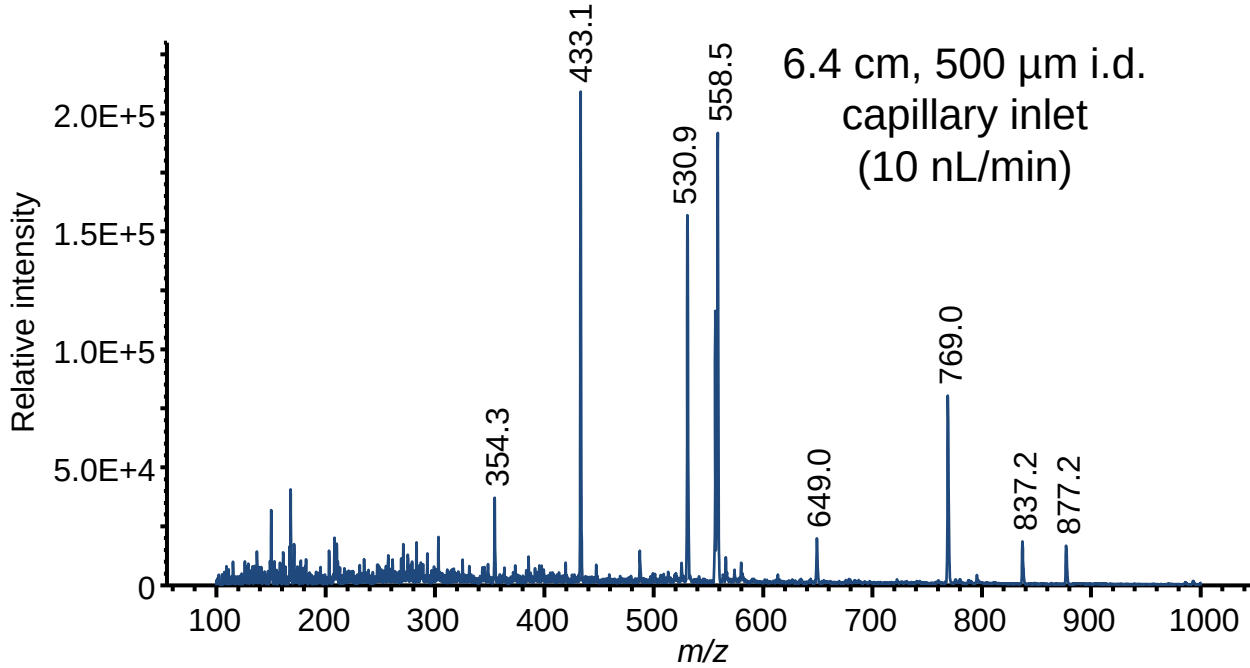
Low pressure ESI chamber to improve desolvation

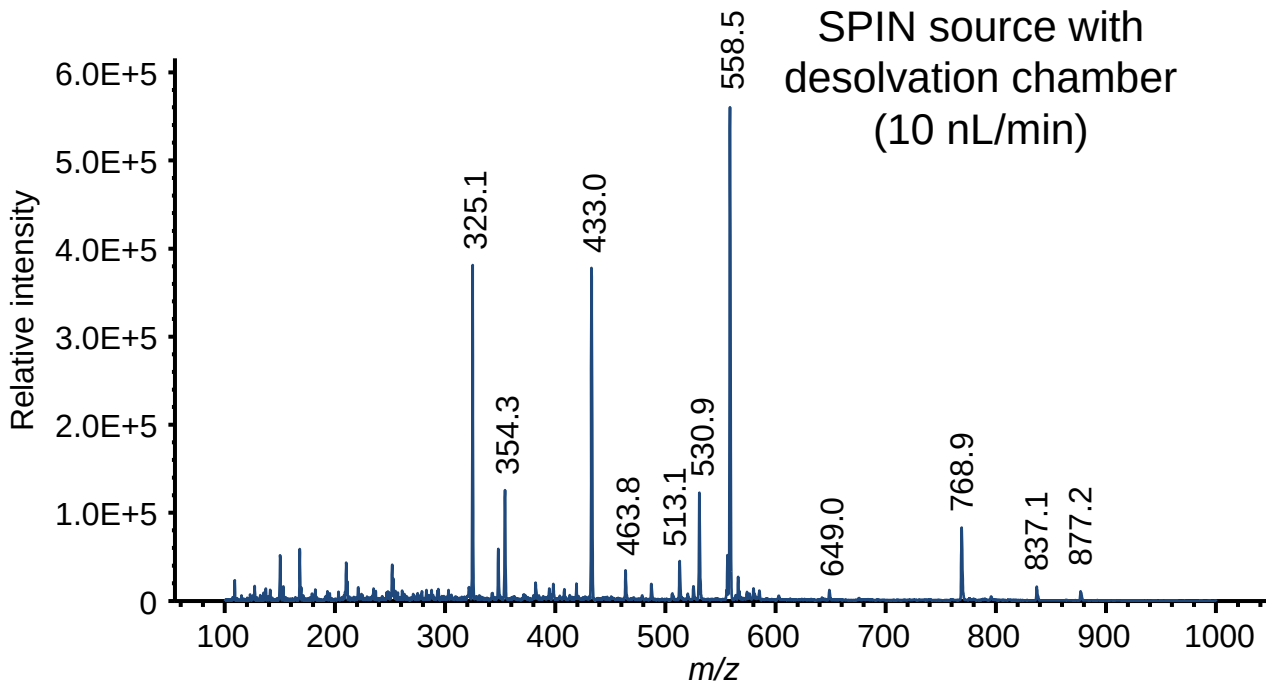


- Provides locally higher pressure (~2 – 4 fold)
- Increased electrospray stability
- Transmission efficiency to ion funnel >90%.

Benefits of the SPIN source with a desolvation chamber

1. Increased electrospray stability at low flow rates
2. Increased sensitivity
3. Reduced background chemical noise
4. Elimination of bias in the inlet capillary e.g. against lower *m/z* species





Summary

- The SPIN source allows stable low-pressure ESI operation and effective ionization, capture, desolvation and transmission into the mass spectrometer
- Eliminates large ion losses at the interface inlet
- Provides high sensitivity with use of higher more robust HPLC flow rates
- Reduces ‘chemical noise’
- Eliminates capillary inlet biases
- Further improvements expected as desolvation is optimized

Acknowledgements

- NIH National Center for Research Resources
- NIH National Cancer Institute
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