High Magnetic Fields in Mass Spectrometry

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Specific Questions

- 1. Can he give a sketch of the ICR community, with respect to their research interests and where they are located (geographically and also with respect to universities/ government labs/industry/magnet labs? Where are the leading ICR research groups, and what do they do?
- 2. What are the most significant applications of ICR in biological, physical, and chemical sciences?
- 3. What are the main technological advances in ICR in the past decade? Who is responsible for these advances (in the research community and in industry)?
- 4. How do the facilities in Tallahassee compare to what is available elsewhere?
- 5. What has the impact of ICR efforts at NHMFL been?
- 6. What needs to be done to take the next steps in improving the technique, and what new magnets would be required?
- 7. Are there technical challenges that limit the sensitivity or applicability of ICR?
- 8. What are the challenges that must be overcome for magnet design (field size, homogeneity, etc)?
- 9. How would higher fields affect ICR measurements and their range of applications?
- 10. What is likely to happen in ICR technology and applications in the next decade?
- 11. Does it make sense for the US to concentrate ICR facilities at NHMFL?

Outline

1. Sketch of the ICR community
2. mini CV
3. Warwick High Field Magnetic Resonance Centre
4. How does FTICR work?
5. Important application of FTICR mass spectrometry
6. Technological advances in FTICR MS in the last decade
7. NHMFL’s impact
8. How would better magnets help FTICR MS? What kind?
9. What other technological advances are needed for FTICR MS?
10. What technological developments can be expected in the next decade?

Sketch of the ICR community

- USA
  - NHMFL, 14.5 T (Alan Marshall, Chris Hendrickson, Ryan Rodgers)
  - PNNL, 15 T (Jean Futrell, Dick Smith, Julia Laskin, Michael Belov, Lilijana Pasa-tolic)
  - UCLA, 15 T (Joe Loo)
  - Washington University at St. Louis, 12 T (Michael Gross)
  - Boston University, 12 T (Catherine Costello, Cheng Lin)
  - Northwestern University, 12 T (Neil Kelleher)
- Korea 15 T (Korean Basic Science Institute)
- UK
  - Warwick 12 T (Peter O'Connor, Mark Barrow)
  - Edinburgh 12 T (Pat Langridge-Smith, Logan Mackay)
- Europe
  - Amsterdam, 9.4 (Ron Heeren)
  - Leiden, 15 T (Andre Deelder)
  - Paris, 9.4 T (Julia Chamot-Rooke)
  - EPFL/ETH, 11.5 T (Yury Tsybin, Renato Zenobi)
  - Munich/Konstanz/Kiel (7 T)
- Moscow (7 T)

- Plus many applications/users

Peter B. O’Connor, mini CV

- PhD 1995 Cornell University with Prof. Fred W. McLafferty
- Postdoc, FOM-AMOLF Amsterdam with Ron Heeren
- 2 years with IonSpec – ICR instrument manufacturer
- 10 years at Boston University
- 3 years with Warwick University

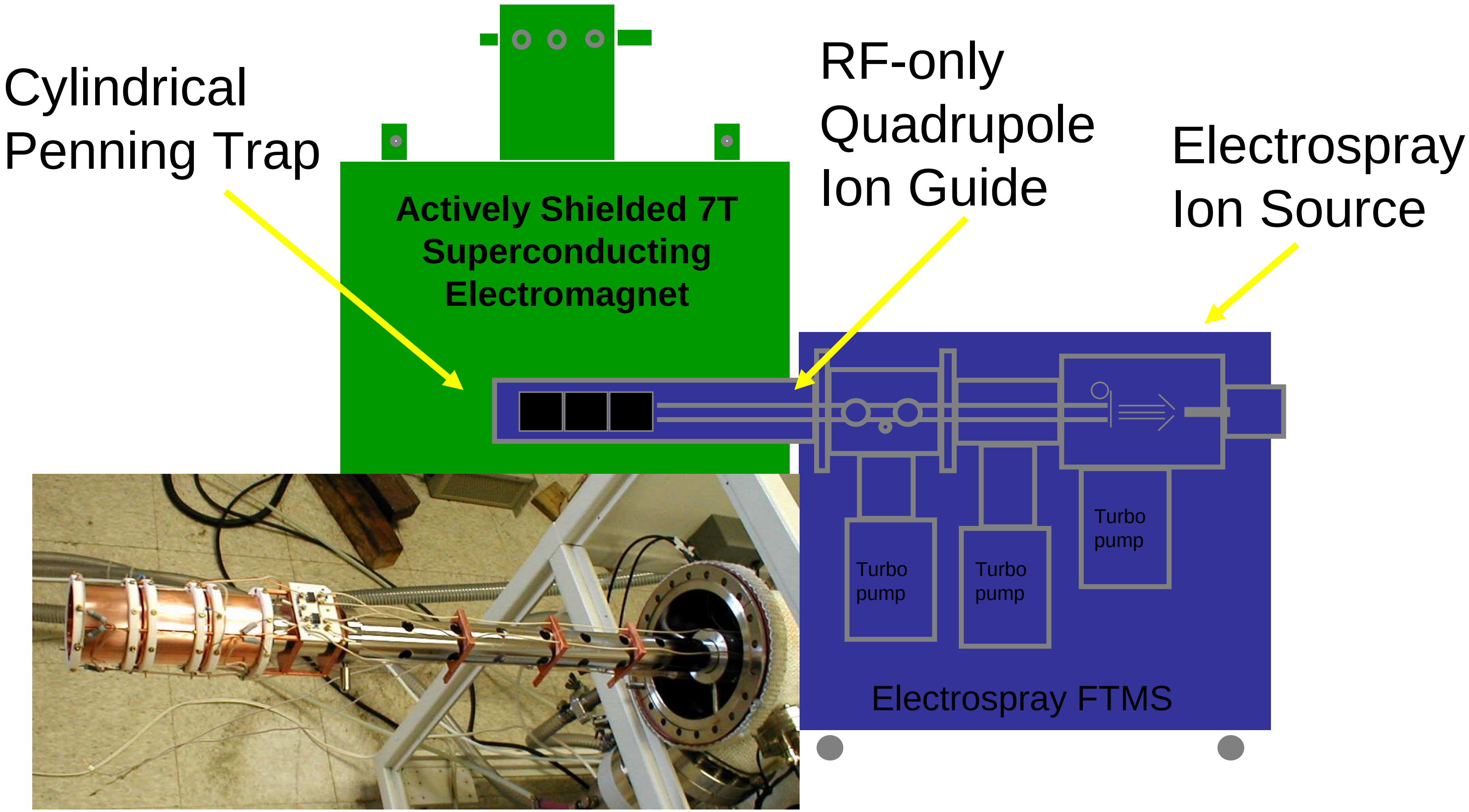
- ~100 publications, h-index ~ 30. (All but 3 in FTICR-MS, I think)
- 3 patents

- Cryogenic FTICR MS, preamplifier design, FDM and frequency shifting, phasing, ExD, thin gate-valve, RF oscillator design, new Gabrielse-cell design
- Isoaspartic Acid analysis in proteins, cisplatin (and related molecule) reactions with proteins, glycation of proteins, polymer analysis by ICR,

Warwick high field Magnetic Resonance Centre

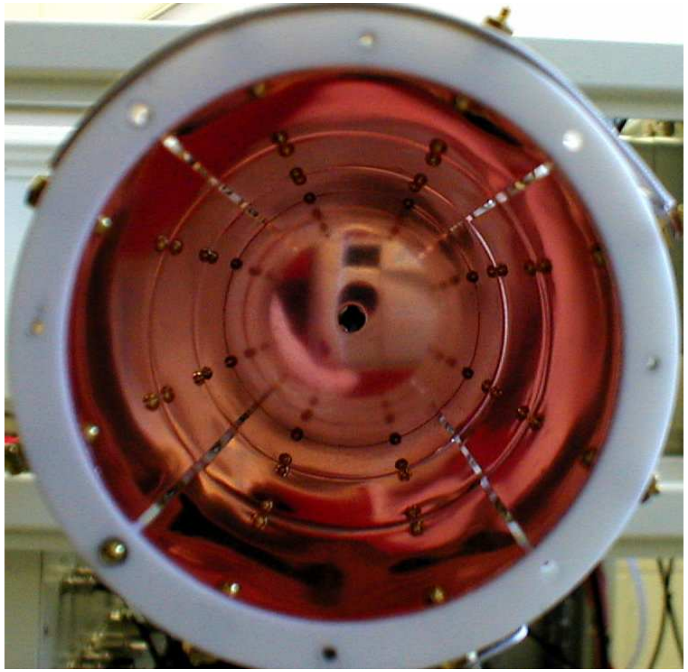
- 850 MHz (19.8T) wide bore
- Dynamic nuclear polarization transfer development rig (2 x 7T and 14T)
- 6 more ss NMR magnets, up to 15T
- 2 x 12T + 5T ICR magnets
- 5 EPR Magnets

How Does FTICR-MS Work?

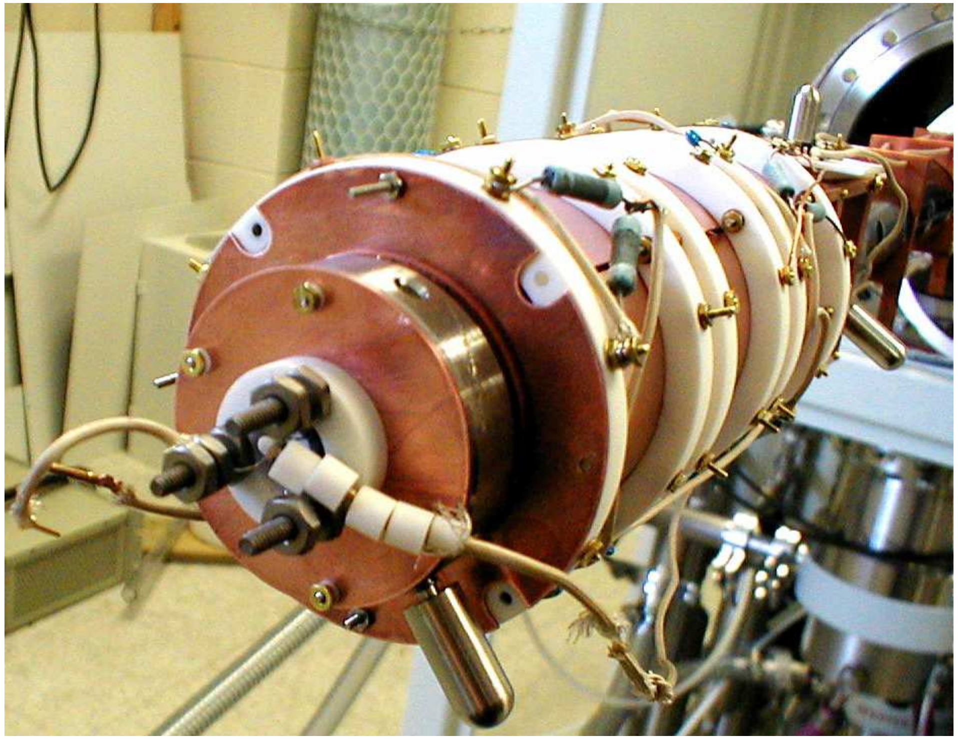


How Does FTICR MS Work?

The Penning Trap



The ions' view of the cell



New ECD gun design using a dispenser cathode

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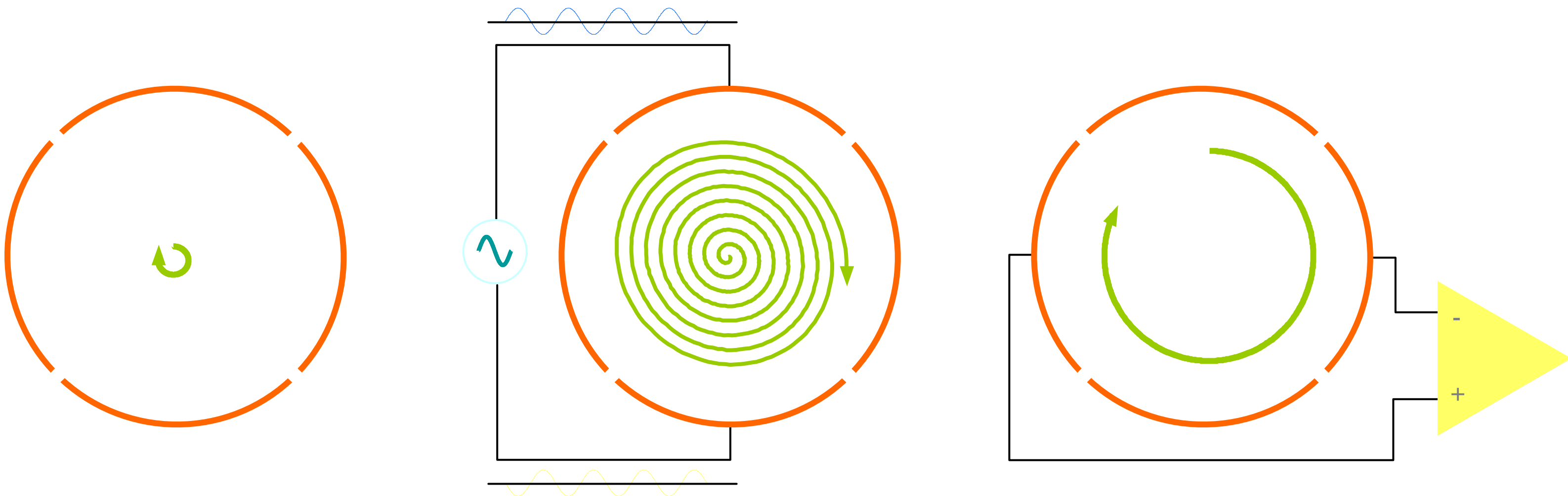
How Does FTMS Work?

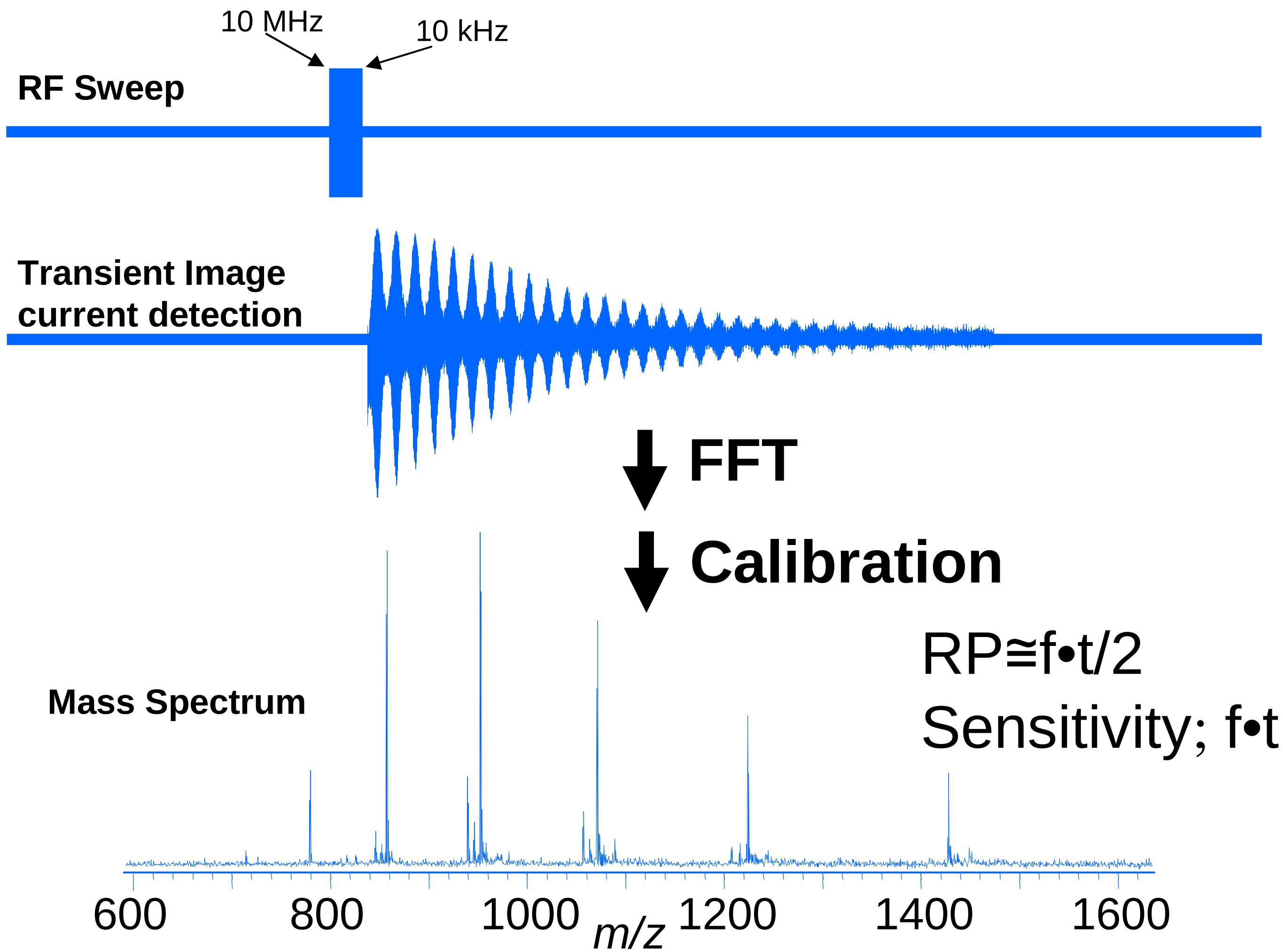


Ions are trapped and oscillate with low, incoherent, thermal amplitude

Excitation sweeps resonant ions into a large, coherent cyclotron orbit

Preamplifier and digitizer pick up the induced potentials on the cell.

How Does FTICR MS Work?



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ICR applications

- Proteomics
  - top-down ☻
  - bottom-up ☺
  - PTMs ☺/☻
- Other-Omics
  - Glycomics ☺/☻
  - Genomics
  - Metabolomics ☺/☻
- Petroleum ☻
- Other complex mixtures
  - Humic acids ☻
  - Metabolites ☺/☻
- Polymers ☺/☻

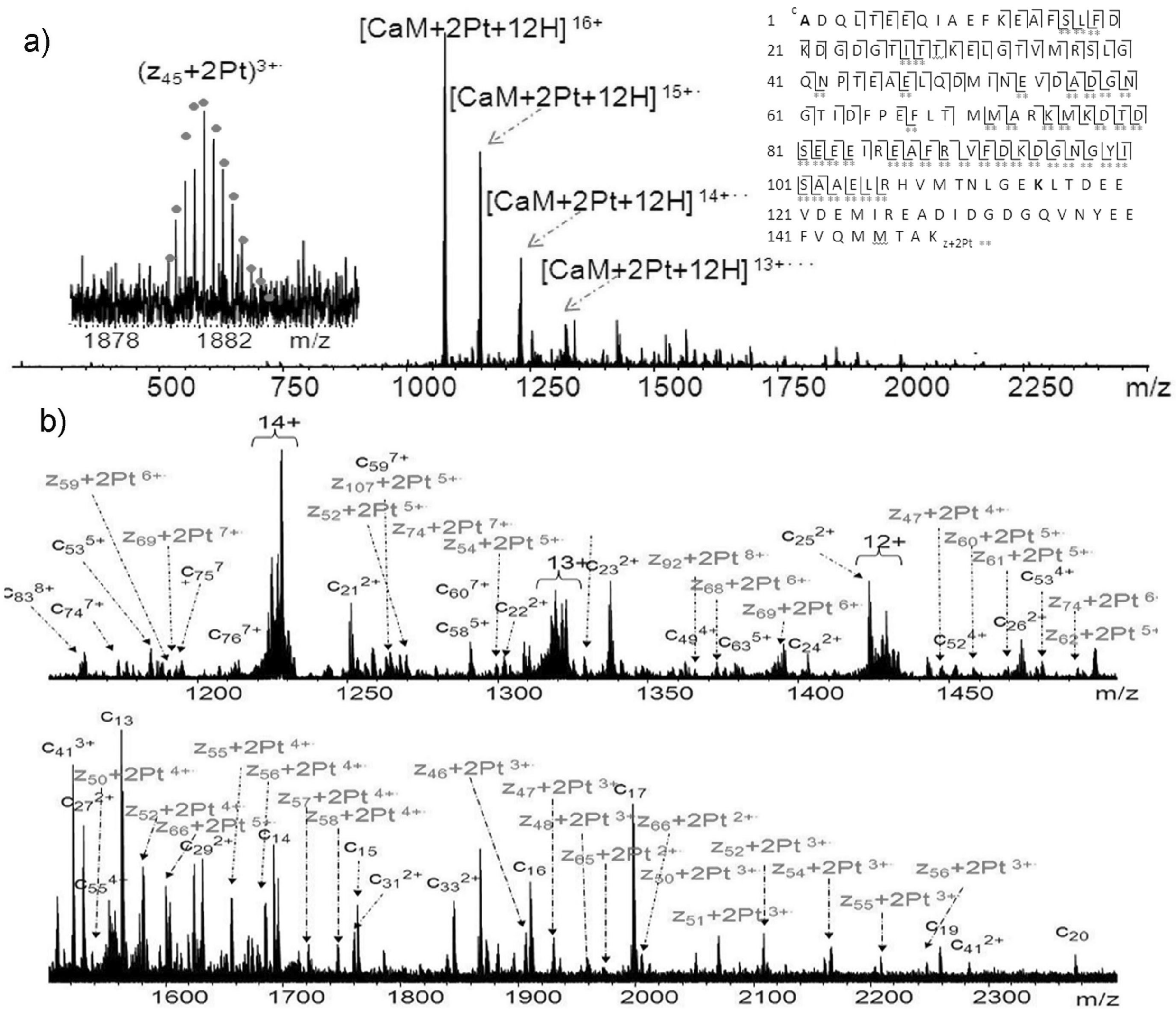
☻ Detailed study of fragmentation mechanisms

☻ Deep study of molecular structure using new methods of fragmentation

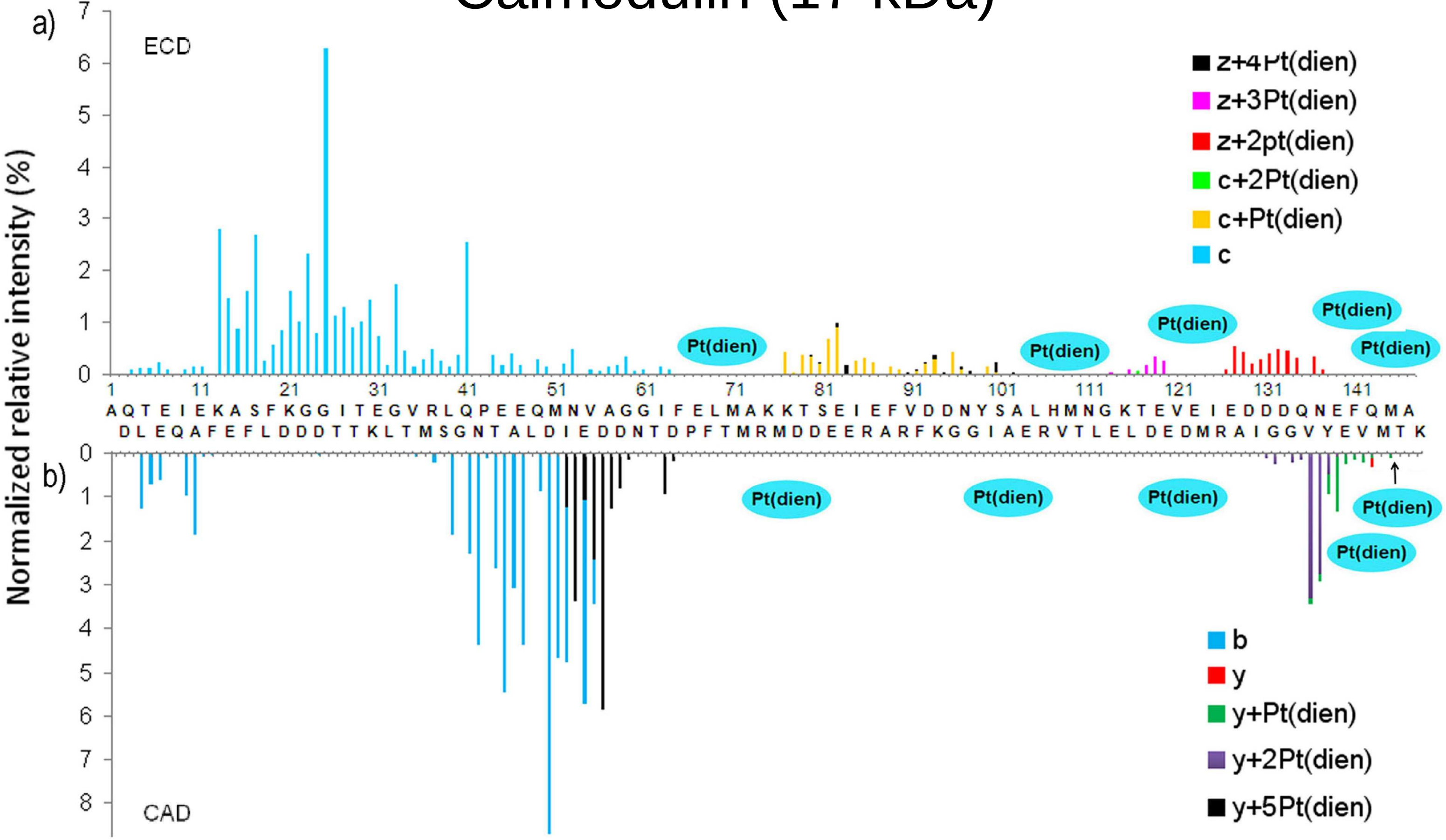
☻ Applications which can "only" be done on an ICR.

☺ Applications which can be done better on an ICR.

Top-down analysis of cisplatin binding to Calmodulin (17 kDa)



Summary of top-down analysis of Pt(dien) binding to Calmodulin (17 kDa)



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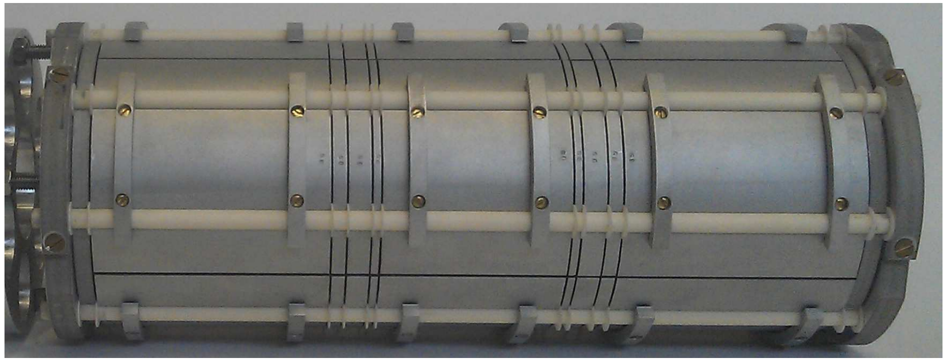
Technological advances in ICR in the past decade.

- New ICR cells (Tolmachev (PNNL), Rempel (WashU), Nikolaev (Moscow), 120° cell(NHMFL), temp-controlled cell (Amsterdam))
- New magnets
  - shielding (magnet companies: Cryomagnetics, Magnex, Oxford, Bruker)
  - higher field (NHMFL, PNNL, and magnet companies)
- Amplifier designs (O'Connor)
- Cryocoolers and cryogen free magnets (Cryomech, Cryogenic Ltd., magnet companies)
  - Cryogenic FTMS (O'Connor)

- Data analysis (McLafferty/O'Connor), phasing (NHMFL/O'Connor), FDM and frequency tracing (O'Connor).
- Excitation control (NHMFL), User-interactive data systems (NHMFL/Amsterdam).
- Calibration (Univ. Georgia, NCSU). PIC simulations (PNNL, Amsterdam, Moscow, Belgium)
- ExD (Zubarev, O'Connor, Cooper, Heeren, Hakansson, Tsybin)
- Gate valve and oscillator designs (O'Connor)
- New ion injection optics (Thermo, Bruker, PNNL)
- Ion-funnels (PNNL), hybrids (Everybody), sources (NHMFL), Imaging (Amsterdam), etc

New ICR cells



Gabrielse/Tolmachev/Rempel cell

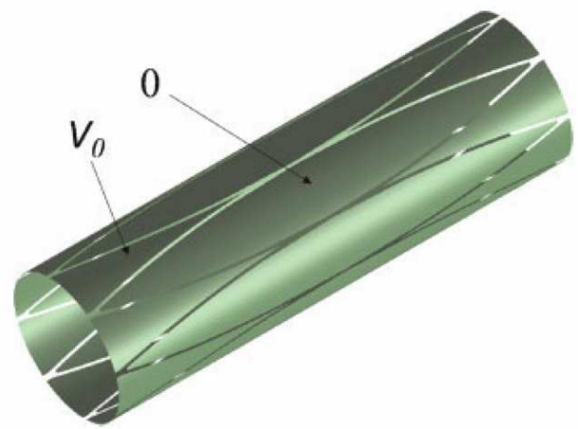


Figure 1. Proposed segmentation pattern for an FTICR cell.

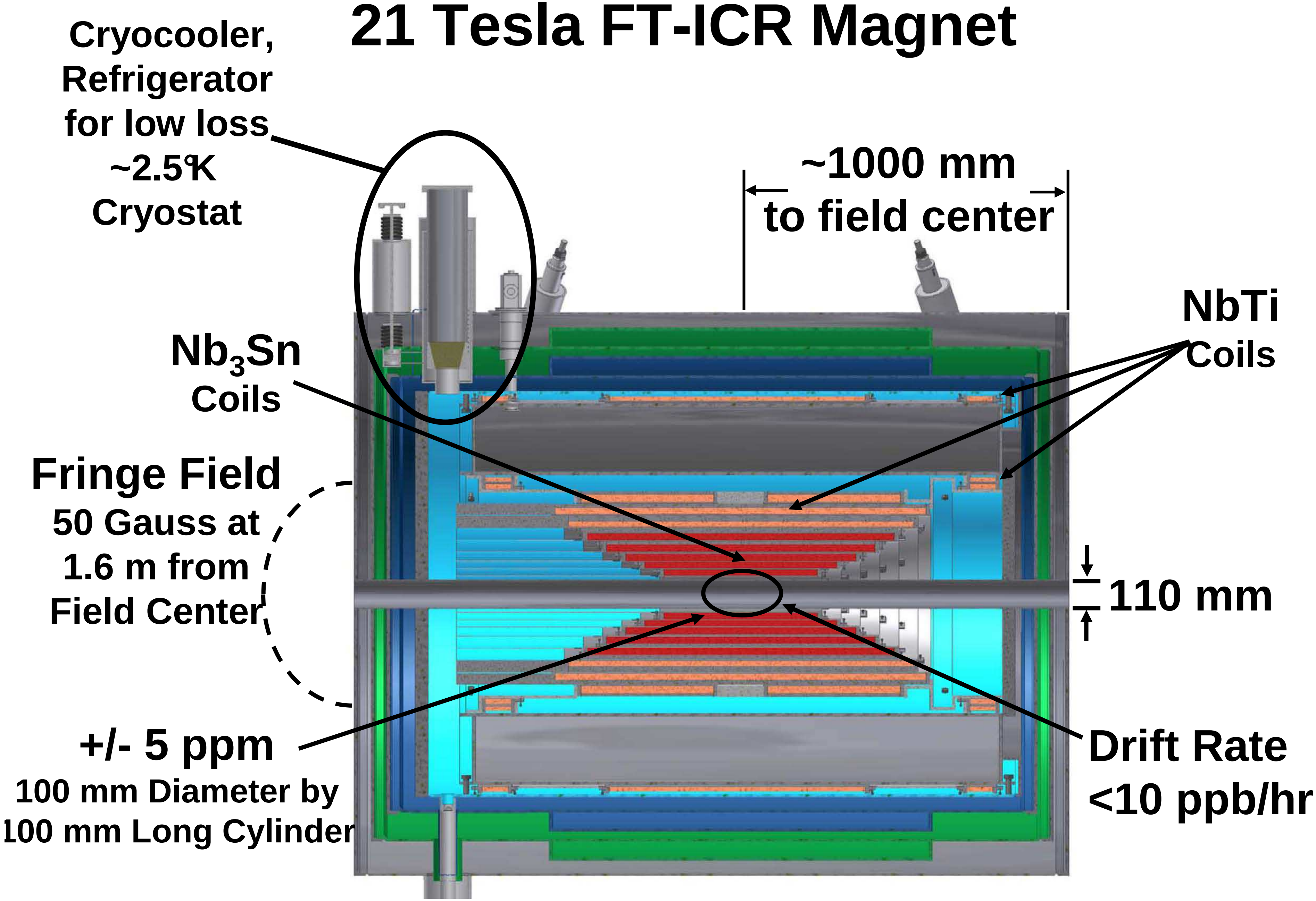
Nikolaev cell

1. Brustkern, A. M.; Rempel, D. L.; Gross, M. L., *J. Am. Soc. Mass Spectrom.* **2008,** *17*, 1281.

2. Tolmachev, A. V., et al., *J. Am. Soc. Mass Spectrom.* **2008,** *19*, 586.

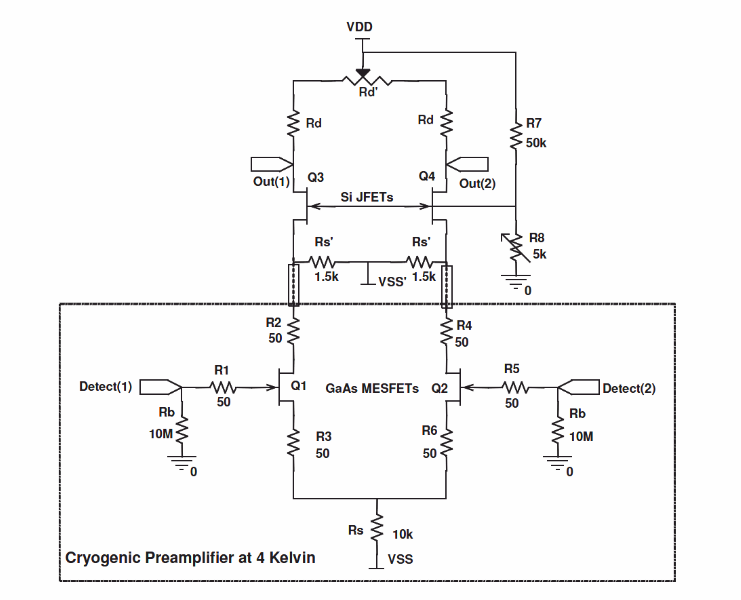
3. Nikolaev, E. N.; Boldin, I. A.; Jertz, R.; Baykut, G., *J. Am. Soc. Mass Spectrom.* **2011,** *22*, 1125.

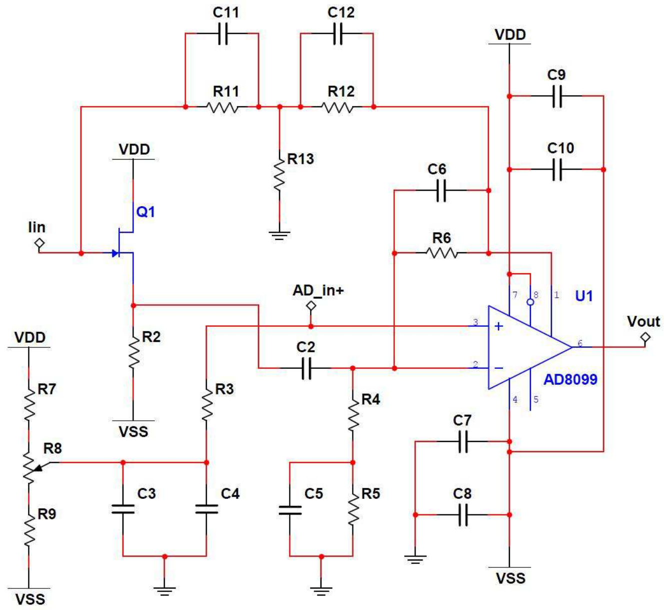
21 Tesla FT-ICR Magnet



slide courtesy of Alan Marshall.

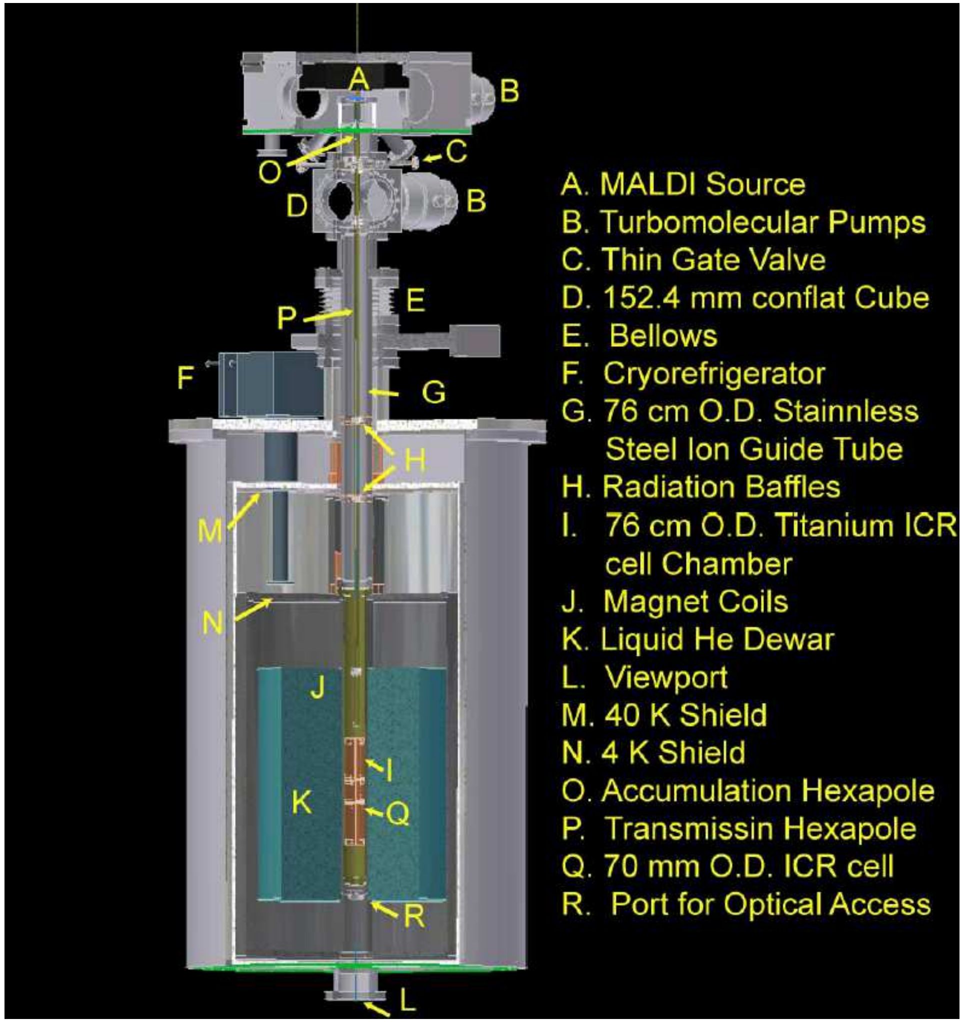
New Pre-Amplifier Designs





1. Mathur, R.; Knepper, R. W.; O'Connor, P. B., *Ieee Transactions on Applied Superconductivity* **2008,** *18*, 1781.
2. Mathur, R.; Knepper, R. W.; O'Connor, P. B., *J. Am. Soc. Mass Spectrom.* **2007,** *18*, 2233.
1. Lin, T.-Y.; Green, R. J.; O'Connor, P. B. Transimpedance Amplifier. UK Patent WO2008103970 **30 March 2012.**
2. Lin, T.-Y.; Green, R. J.; O'Connor, P. B., *Rev. Sci. Inst.* **2012**, submitted.
3. Lin, T.-Y.; Green, R. J.; O'Connor, P. B., *Rev. Sci. Inst.* **2011,** *82*, 124101.

Cryogenic FTICR Mass Spectrometer



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What has been the impact of the ICR research at NHMFL?

- Higher field
  - First 9.4T system (1995)
  - First 15T system (2000)
  - 21T system (current development)
- Petroleum analysis + APPI and other ionization methods (2000-current)
- Phasing (10+ publications since 1975)
- 120° cell, radial positional programming (2011)
- First qQqFTMS (1996)
- Data system development (1996 – current)

- Overall, consistent, sustained, and directed development toward improving FTICR mass spectrometry instruments.
- Extremely high productivity/publication rate.
- Alan G. Marshall: 750 publications, h~70. 450 publications since moving to Tallahassee.

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How do facilities at NHMFL compare?

- 14.5 T magnet, 9.4 T widebore and 9.4 T, 7T.
- 9.4T and 7T instruments
- 14.5T Thermo instrument
- 21T in development
  - Bruker instrument?

Machining (A+)

Software development (A+)

Electronics (A-)

Magnets (A+)

ICR Personnel (A+)

Does it make sense for the US to concentrate ICR facilities at NHMFL?

- Yes. Marshall has been productive, it's good value for money.
- There's concern that strong funding of ICR at the magnet lab will limit NSF funding for other ICR researchers.
- NHMFL needs to focus on fundamental improvements to the instruments, in addition to higher field.
- They should be working more with the community – like the NMR workshops – with a pre-defined goal to design the ***best possible*** instruments and software.
- Collaborations with companies should be examined in terms of whether the resulting instruments are the best instruments possible. Usually, instrument companies have a different set of priorities.

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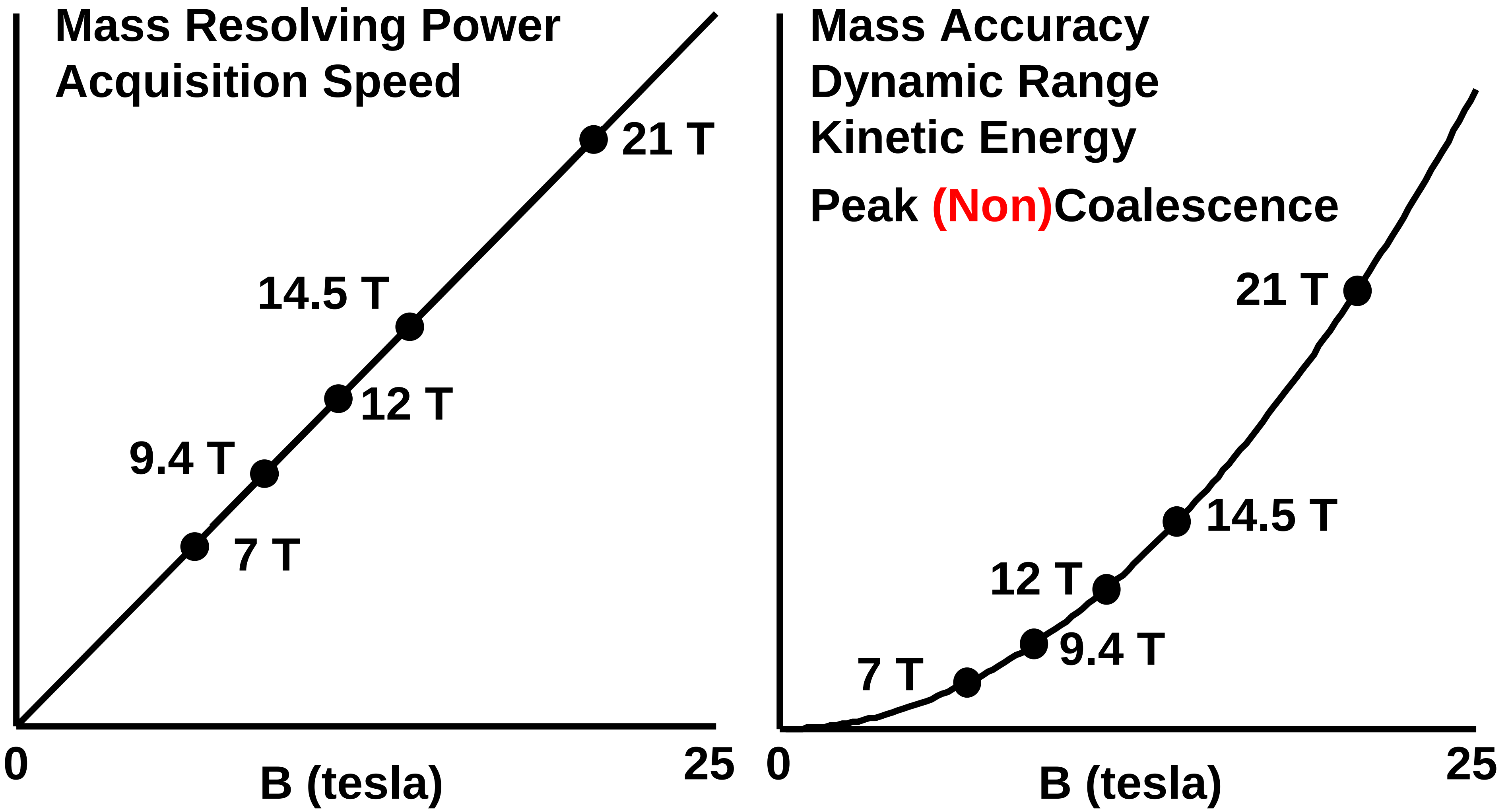
How would higher fields affect ICR measurements and their range of applications?

- Marshall plot.
- top-down, drilling deeper.
- petroleum, dynamic range.

Advantages of High Magnetic Field



Marshall and Guan, *Rapid Commun. Mass Spectrom.* 1996, 10, 1819-1823

slide courtesy of Alan Marshall.

Phasing only provides 1.4-2x improvement, but….

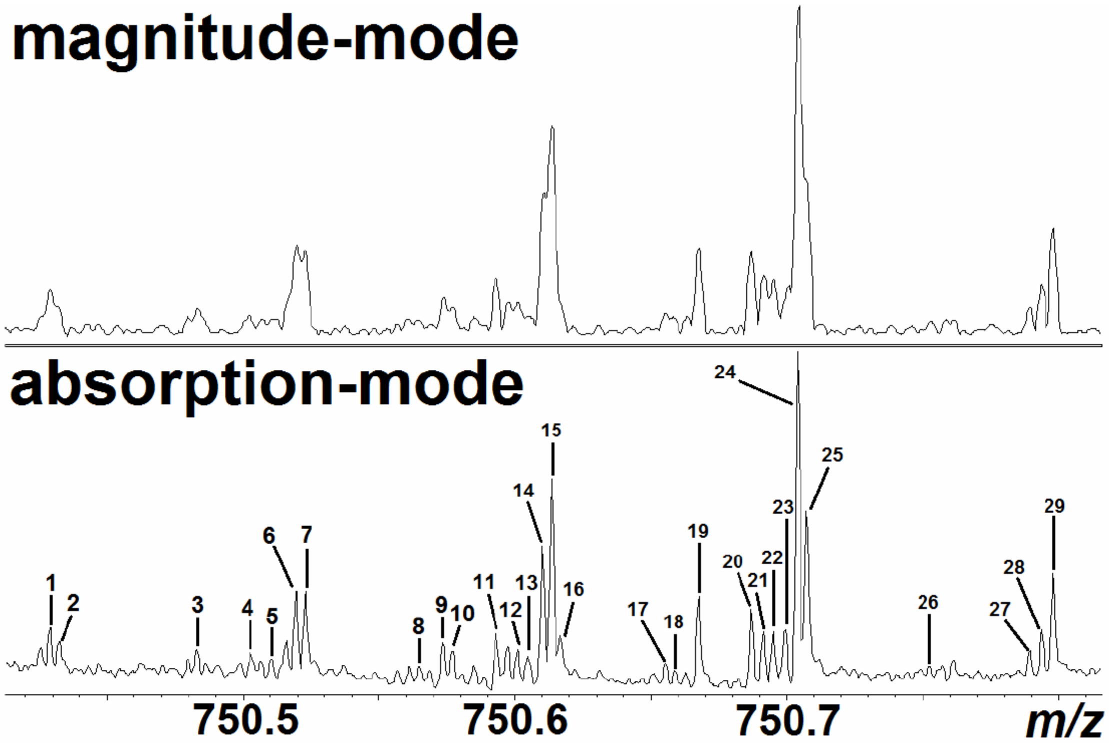
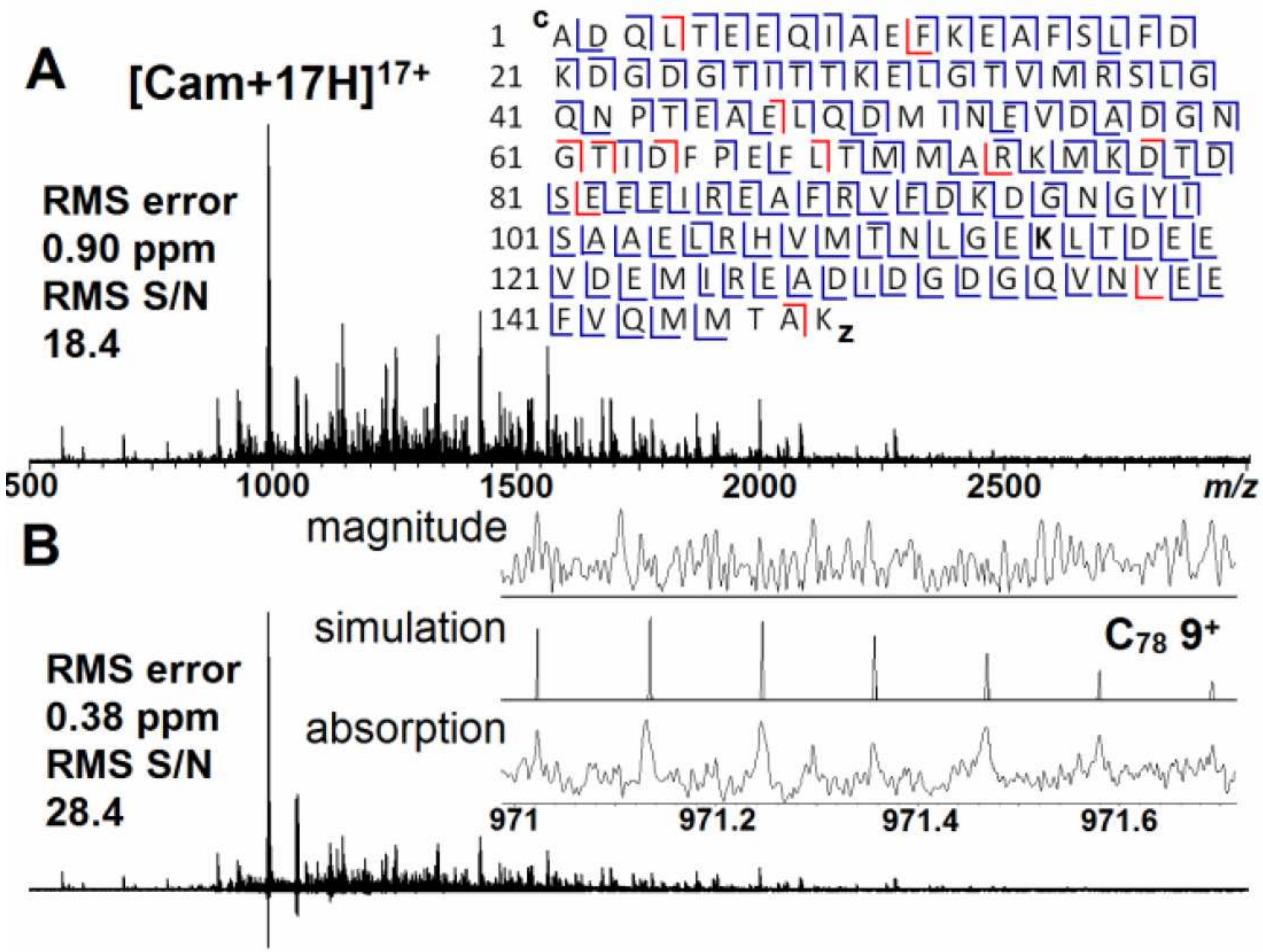


Figure 6. Resolution improvement in absorption mode compared to magnitude mode for a petroleum sample.



A. Unphased absorption mode spectrum of the top-down Electron Capture Dissociation tandem mass spectrum of calmodulin, a 17 kDa protein, and B. the same spectrum after calculation of the absorption mode.

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Room for Improvement

- Resolution, typical broadband RP=250,000, best case RP=20,000,000
- Mass Accuracy, typically 0.2 ppm (internally calibrated and space charge limited), best case 0.1 ppb
- Sensitivity,
    - In cell, typically a couple hundred charges, best case 1 charge
    - From source, typically mid femtomole range, best case 30 zeptomoles

What currently limits performance?

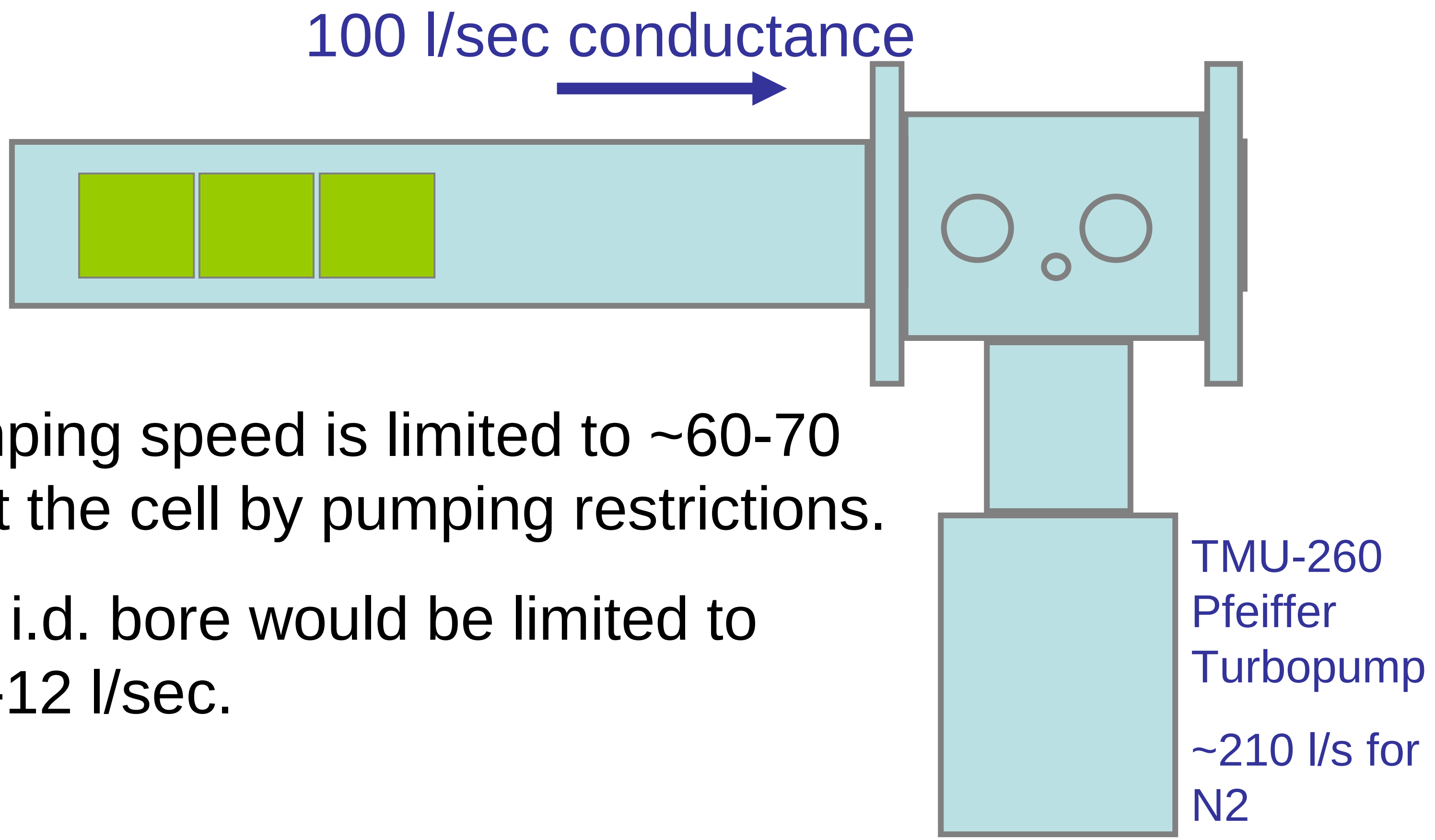
Magnet Limit

Modern FTMS uses 7 T - 15 T magnets. NMR uses 600 MHz (14 T) to 900 MHz (21 T) magnets.

MRCA 400MHz/54mm/AS	9.4 T
MRCA 400MHz/62mm	
MRCA 400MHz/89mm	
MRCA 400MHz/89mm/AS	
MRCA 400MHz/150mm	
MRCA 500MHz/52mm	11.7 T
MRCA 500MHz/54mm/AS	
MRCA 500MHz/89mm/AS	
MRCA 500MHz/89mm	
MRCA 500MHz/123mm	
MRCA 500MHz/123mm/AS	
MRCA 600MHz/52mm	14 T
MRCA 600MHz/54mm/AS	
MRCA 600MHz/89mm	
MRCA 600MHz/89mm/AS	
MRCA 700MHz/54mm/AS	16.3 T
MRCA 700MHz/89mm	
MRCA 750MHz/54mm	17.5 T
MRCA 750MHz/89mm	
MRCA 800MHz/52mm	19.7 T
MRCA 800MHz/89mm	
MRCA 900MHz/52mm	21 T
MRCA 900MHz/62mm	

Cost and difficulty of high homogeneity magnet production scales with bore diameter.

Pressure Limit



Pumping speed is limited to ~60-70 l/s at the cell by pumping restrictions.

A 2” i.d. bore would be limited to ~10-12 l/sec.

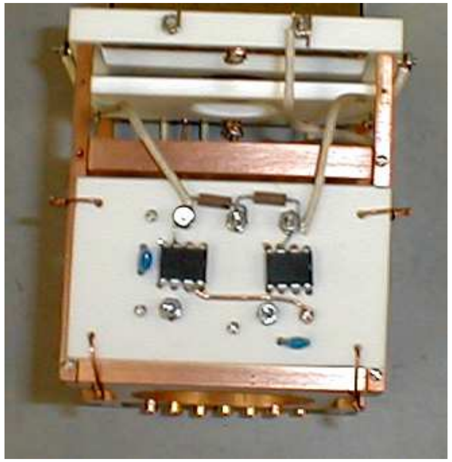
Preamplifier Noise Limit

FTMS preamplifiers are thermal-noise limited.

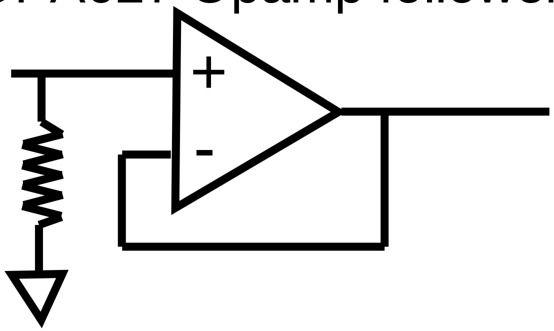
$$V_{noise}(rms) = \sqrt{4 k_b T R B}$$

Best case (G. Anderson) 100 charges ≅ 3 s/n.

In-Vacuum preamplifer



OPA627 Opamp follower



6 MΩ resistor

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What needs to be done to take the next steps in improving the technique, and what new magnets would be required?

Magnet improvements:

- Magnets (higher field and higher homogeneity volume – longer?)
- Cold bore designs?
- Helium usage (cryogen free magnets)

ICR improvements:

- Cell homogeneity (E and M)
- Solving the space charge issue
- Better amplifier designs
- Base pressures.

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What is likely to happen in ICR technology and applications in the next decade?

- Technology = single charge sensitivity, 21T magnet, better ICR cells
- Better data systems = more flexible experiments, streaming and bigger data sets, better data analysis software
- Exact mass data analysis and more….

- Applications = more complex mixtures, more depth to the complex mixture analysis currently done
- Polymers?
- IR spectroscopy (Oomens/Rizzo)
- Ion Mobility

fini.