Ultrafast FAIMS/MS Analyses at Extreme Electric Fields in Multichannel Microchips

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Field Asymmetric Waveform IMS (FAIMS) or Differential IMS

a) Basis:

\[ K(E) = K(0)[1 + a(E/N)^2 + b(E/N)^4 + \ldots] \]

\( K \) - mobility, \( E \) - electric field, \( N \) - gas density

Measures the difference between mobilities at high and low \( E \)

b) Operation:

\[ \Delta x = K_D E_D \Delta t_h - K_l E_l \Delta t_l = (K_h - K_l) E_D \Delta t_h \]

Typical \( E_D \sim 25 \text{ kV/cm} \) (~100 Td)

Gap widths (\( g \))

~2 mm (Thermo): voltage ~4 kV
0.5 mm (Sionex): voltage ~1.2 kV

FAIMS output: CV spectrum
Why Stronger Dispersion Field in FAIMS?

Better resolution (at equal separation time)

Resolving power: \[ R = \frac{E_C}{w} \]

Compensation field \( E_C \) scales as dispersion field \( E_D \) cubed (to the 1st order)

Peak width (planar gaps): \[ w = \frac{4}{K} \sqrt{\frac{D_{II} \ln 2}{t}} \]

Diffusion constant \( D_{II} \)
Separation time \( t \)

Diffusion depends on the field intensity also

Low-field limit
High-field limit
\[ D_{II} = \frac{kTK}{q} \quad D_{II} \text{ proportional to } E_D^2 \]

Resolving power scales as square to cube of \( E_D \)
(observed in experiments)
More Reasons for Stronger Dispersion Field in FAIMS

Faster analyses

Resolving power proportional to $E_C$ linearly but to $t^{1/2}$

$$R = \frac{E_C}{4} \frac{K}{\sqrt{\frac{t}{D_N ln 2}}}$$

Thus separation speed at same $R$ scales as $E_D^4 - E_D^6$!

Doubling $E_D$ (to 200 Td) would accelerate FAIMS by 1 - 2 orders of magnitude

Scanning FAIMS could be inserted into LC/MS without slowing LC

Separation flexibility

FAIMS separation depends on all terms:

$$K(E) = K(0)[1 + a(E/N)^2 + b(E/N)^4 + \ldots]$$

Higher terms more important at greater $E$

ions with close $a$ often have dissimilar $b$ (J. Phys. Chem. A 110, 2663, 2006)

Species “co-eluting” at lower $E$ may be distinguished at higher $E$
Limitations on the Dispersion Field

Fundamental

Collisional heating destroys ions

Heating $\Delta T$ proportional to $E_D^2$:

$$T_f = T + \Delta T = T + MK^2E^2/(3k)$$

Causes isomerization of fragile ions (e.g., proteins) in FAIMS at 80 Td, with maximum $\Delta T \sim 50$ °C (Anal. Chem. 79, 1523, 2007)

Normally no fragments in FAIMS spectra - can increase $E_D$ in general

200 Td means $\Delta T \sim 300$ °C - often survivable (at least, for a short time)

Engineering

Electrical breakdown of gas

Maximum voltage depends on the gap width, gas identity, and pressure

In air (1 atm): 7 kV ($\sim$140 Td) at $g = 2$ mm, 2.3 kV ($\sim$180 Td) at 0.5 mm

Paschen curves sublinear: narrower gaps allow stronger fields!

Narrowing the gap removes this limitation
Multichannel FAIMS Microchips

Manufactured by semiconductor process (silicon + gold plating)

Gap dimensions (mm)
width  depth  total length
0.035  0.3    120

Serpentine gap cut into 8 mm² area
(50% open surface)

Breakdown voltage in air = 600 V (field of 700 Td)
Stand-Alone FAIMS

- β-radiation source (Ni$^{63}$)
- Gas flow rate $Q \sim 2 - 3\ \text{L/min}$
- Sample diluted by re-circulating exhaust
- Dispersion voltage 212 V (250 Td)
- After FAIMS, ions detected on a grid (8 mm$^2$) biased at 30 V

Separation time
$\sim 15 - 25\ \mu\text{s}$
(2 - 4 ms in Sionex units, 100 - 200 ms in Thermo)

Waveform close to bisinusoidal

“Lonestar”

E/E

22 - 28 MHz

Time, ns

0 10 20 30 40 50 60 70 80 90
Evaluation (Positive Ions)

Vapor of DMMP (124 Da) - simulant of CWA much studied by FAIMS

$E_D/N$ up to 220 Td at 0.51 atm (Sionex data)

$E_C/N$, Td

Monomer

Dimer

RIP

Relative intensity scale

0.0 0.5 1.0 1.5 2.0

Peak positions at same $E_D$ match previous work

As predicted by simulations, resolving power $\sim 40 - 50\%$ of macroFAIMS

Suffices for many applications
Inversion of Ion Type

Ions in FAIMS typed A, B, or C

Vapor of DNT (182 Da) - common explosive in anion mode

Theory
Transition to type C inevitable at high enough $E_D$
($A. A. Shvartsburg, CRC Press, 2008$)

Many ions of type A in previous work change to type C
**Coupling to MS**

Chip inserted into ESI/MS using curtain plate/orifice interface in front

\[ Q = Q_{\text{out}} + Q_{\text{ms}}; \]
\[ Q_{\text{cu}} = Q_{\text{in}} - Q_{\text{out}} - Q_{\text{ms}} \]

Defines separation time and thus resolution

Controls ion desolvation prior to FAIMS

Varying \( Q_{\text{in}} \) and \( Q_{\text{out}} \) gives independent control of resolution and desolvation
Effect of Varying Instrumental Parameters

For reserpine (1+)

$E_C$ scales as $E_D^3$

Peaks narrow at lower flow through the chip, $R$ scales as $t^{1/2}$

Trends match theory, simulations work at extreme fields
Filtering a Complex Sample

ESI of amino acid solutions produces protonated monomers and dimers

FAIMS may improve s/n by over an order of magnitude (similar to previous systems)

Leucine dissolved in lab wastewater

FAIMS may improve s/n by over an order of magnitude

s/n increased ~20 times

Chemical noise

x 20
Using He/N₂ Mixtures

**Foundations**

He/N₂ mixtures with ~50% He commonly improve FAIMS separation, because of non-Blanc phenomena ([Anal. Chem. 76, 7366, 2004](https://doi.org/10.1021/ac402889h)).

Effect to decrease at higher $E_D/N$, as ion collisions with all molecules become harder.

Different gases (or mixtures) should produce closer results than in “macro-FAIMS”

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**Data at 250 Td**

For reserpine:

$E_C$ shift of <20% vs. ~100% at 80 Td

In N₂:

Incomplete separation of Fib and Bk peptides

In 1:1 He/N₂:

Peaks shift by ~30% (vs. ~100% at 80 Td)

Separation at low flow

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Variation of gas (incl. use of He/N₂ mixtures)

less effective than previously, still helps
**Summary**

- Narrowed the FAIMS gap by 15 times to double the field to >60 kV/cm
- Accelerated separation by ~100 times, to ~20 - 40 µs per CV value. Whole CV scan obtainable in ~1 ms, CV/DV map in ~20 ms. LC/FAIMS/MS analyses possible even with fastest LC gradients
- With ions partitioned into ~50 channels and filtered rapidly, current capacity of FAIMS greatly increased
- ESI/FAIMS/MS integrated using curtain plate/orifice interface

**Challenges and further Work**

- Resolution lower than with “macro-FAIMS” by 2 - 2.5 times, precludes many applications
- Effect of varying the gas less than in macro-FAIMS, limits the options to improve separation by optimizing the gas
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