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3-dimensional micro-gas chromatography device for rapid and sensitive indoor air chemical exposure assessment

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Outline

• Challenges for indoor (S)VOC assessment

• Introduction
  – Gas chromatography (GC)
  – Micro-GC (μGC)
  – Comprehensive 2-D GC/μGC (GC x GC or μGC x μGC)

• Smart multi-channel multi-dimensional GC
  – Concept
  – Comparison
  – On-column vapor detectors
  – 2-D smart GC
  – 3-D smart GC

• Proposed project
Challenges for indoor (S)VOC assessment

1. Large number of (S)VOCs to be quantified
   Cleaning products, pesticides, etc.
   Interference background

2. Temporal variations

3. Spatial variations

**An instrument should be**
1. Able to analyze many (S)VOCs
   • qualitatively (type of molecule)
   • quantitatively (how much)

2. Portable (in-situ measurement)

3. Rapid (temporal measurement)
Introduction
Gas chromatography (GC) + Mass Spectrometer

- Best analytical tool to analyze hundreds of volatile organic compounds (VOCs)

- High peak capacity
- Long analysis time
- Heavy and bulky
- Needs dedicated personnel
- High power consumption
GC on a chip
Micro-GC (μGC) or portable GC

- First demonstrated in 1979 (first lab-on-a-chip device)
  Terry et al., IEEE Trans Electron Devices, ED-26, 1880 (1979)

- Portable
- Rapid analysis
- Less power consumption
- Can be automated
- Low chromatographic resolution and peak capacity → co-elution
General concept of multi-dimensional separation

- 2-D gel electrophoresis as an example
- Two independent separations based on two distinct properties (e.g., charge and mass)
- Enhanced separation capability or resolution

Total peak capacity = $N_1 \times N_2$

- $N_1$: peak capacity for 1\textsuperscript{st} separation
- $N_2$: peak capacity for 2\textsuperscript{nd} separation
Multi-dimensional GC

How to translate the 2-D (or higher-dimensional) gel electrophoresis concept to 2-D GC?

Difficulties:
- Vapors are difficult to be held in place

A naïve idea: Parallel connection

A more practical implementation: Series connection
Comprehensive 2-D GC or μGC (GC x GC, μGC x μGC)

- **1st-dim column**: long (5-30 m), coated **non-polar** stationary phase
- **2nd-dim column**: **very short** (0.5-1 m), coated with **polar** stationary phase
- Vapor molecules undergo two separations by vapor pressure and polarity
- Total peak capacity = $N_1 \times N_2$ (**ideally**)

Working principle of GC x GC or \( \mu \)GC x \( \mu \)GC

- Pneumatic modulator
- Thermal modulator (more popular)

Modulator period: 1-10 seconds

Comments on GC x GC (or μGC x μGC)

**Advantages:**
- Improved peak capacity ($N_{GCxGC} > N_{GC}$)

**Drawbacks:**
1. Reduction of $n_1$ by a factor of $\sqrt{1 + 0.5(P_M / \sigma_{1,0})^2}$ due to modulation (sampling theory)
   - $P_M$: modulation period; $\sigma_{1,0}$: unmodulated peak width from the 1st-dim column
2. Insufficient 2nd-dimensional separation (low $n_2$)
   - Limited by the modulation period
   - Only a few seconds in order to avoid wrap-around issue
3. Peak capacity below theoretical prediction of $N_1 \times N_2$.
   - $N_{GCxGC}$ is only 5-10X better than $N_{GC}$ (under optimal condition)
4. Complicated 2-D chromatogram re-construction
   - Has only one end-column detector
5. Difficult to scale up for higher dimensional separation

Scale up to GC x GC x GC

- 1st-dim column: long (25 m), coated intermediate polar stationary phase
- Modulation #1 period: \(~5\) seconds
- 2nd-dim column: shorter (5 m), coated with non-polar stationary phase
- Modulation #2 period: \(~0.2\) seconds
- 3rd-dim column: shortest (0.55 m), coated with polar stationary phase
- Peak capacity: \(N_1=175, N_2=5, N_3=4\) \(\rightarrow\) Total peak capacity = 3500 or 58/min

Comments:
1. Doable, but benefit is diminishing?
2. Very complicated hardware and 3-D chromatogram re-construction
3. More stringent requirements on higher-dimensional separation (e.g., very short separation time)
4. Rarely explored

Some general thoughts on current GC² and GC³

**Problem:** Information about the 1ˢᵗ-dim (or low dimension) separation is missing

**Current solution:** We rely on a modulator and a detector at the end and to figure it out
Re-construction of 1-dim requires sufficient 2-dim separation

**Problem:** 1ˢᵗ-dim and 2ⁿᵈ-dim separation are not completely independent. They are connected through a modulator
→ Conflicting requirements
• Short modulation period for better 1ˢᵗ-dim separation re-construction
• Long modulation period for better 2ⁿᵈ-dim separation

**Current solution:** We try to optimize or balance the 1ˢᵗ- and 2ⁿᵈ-dim separation

**Why do we need a modulator?**
• To sample the elution from the 1ˢᵗ-dim separation and provide the 1ˢᵗ-dim retention time

**Is it necessary?**
Revisit 2-D gel electrophoresis

- 1st- and 2nd-dim separation are independent
- 1st-dim separation can be measured directly
- No modulator, no re-construction
Revisit the interface between two separations

Detect & Route

1st-dim separation

2nd-dim separation

2nd-dim separation

Works as a phone operator
New concept of smart multi-channel multi-dimensional micro-GC

Non-destructive flow-through on-column vapor detector
- Rapid, sensitive, no interference with the flow
- Watch, but not touch
- No additional dead volume
Examples of smart 2-D and 3-D GC architectures

(A) 1x3-channel 2-D micro-GC

(B) 1x2x4-channel 3-D micro-GC
Working principle

Using 1x2-channel 2-D micro-GC for illustration
Advantages

1. No modulation on the low-dimension effluent
   - No broadening
   - Entire analyte (not just a slice of it) will be sent to the next separation (improved detection limit)

2. Long high-dimension separation (adjustable dynamically)
   - $N_{total} = N_1 \times N_2 \times N_3 \ldots$
   - $N_2, N_3$ can be large, not limited by the modulation period
   - Can do temperature ramping

3. No thermal modulator is needed. Only simple thermal injectors are needed.
   - Simple and robust, easy to fabricate, less power consumption

4. Easy construction of multi-dimensional chromatogram
   - Directly read from the vapor detectors

5. Cascadable
   - Can scale up to 3-D, 4-D, etc. by simply adding more columns to the preceding columns
   - Independent control of each dimension of separation

6. Versatile
   - General purpose instrument
   - Tailored for specific analytes
Comparison (1)

Heart-cutting technology

1\textsuperscript{st}-dim separation ($n_1$)

2\textsuperscript{nd}-dim separation ($n_2$)

Total peak capacity = $N_1 + N_2 \times M$ (M: # of cuts)
## Comparison (2)

### Multi-dimensional GC

- **Heart-cutting**: A few times. Each cut contains multiple peaks. Pre-determined window selection. Window width is 50-100 seconds depending on applications.

- **Smart GC**: \(N_1\) times. Each cut has one peak. Informed decision made by the system. Window width is dynamically adjustable depending on the peak width.

- **GC x GC**: \(3 \times N_1\) times. Each cut has 1/3 peak. Periodic window blindly, even without analyte. Window width is approximately 1-10 seconds.
Comparison (3) - Comparison

<table>
<thead>
<tr>
<th>Isothermal operation</th>
<th>Total peak capacity</th>
<th>Total assay time</th>
<th>Peak capacity production</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comp. GC^2</td>
<td>19968</td>
<td>100 min</td>
<td>200/min</td>
</tr>
<tr>
<td>Comp. GC^3</td>
<td>87360</td>
<td>100 min</td>
<td>874/min</td>
</tr>
<tr>
<td>1x2 smart GC^2</td>
<td>38828</td>
<td>100 min</td>
<td>388/min</td>
</tr>
<tr>
<td>1x2x4 smart GC^3</td>
<td>570000</td>
<td>108 min</td>
<td>5278/min</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Temperature ramping operation</th>
<th>Total peak capacity</th>
<th>Total assay time</th>
<th>Peak capacity production</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comp. GC^2</td>
<td>11018</td>
<td>15 min</td>
<td>735/min</td>
</tr>
<tr>
<td>Comp. GC^3</td>
<td>79560</td>
<td>60 min</td>
<td>1326/min</td>
</tr>
<tr>
<td>1x2 smart GC^2</td>
<td>502600</td>
<td>100.8 min</td>
<td>4984/min</td>
</tr>
</tbody>
</table>
Development of flow-through on-column vapor detectors
On-column flow-through vapor sensors (Overview)

Requirements:
- Non-destructive
- No interference with gas flow
- No or minimal dead volume

Possible candidates:
- TCD (thermal conductivity detector)
- SAW (Surface acoustic wave detector)
- Chemi-resistor
- Chemi-capacitor
- Nanoelectronics (graphene, nanotubes)
- Optical vapor sensors
  - Optical ring resonator (fabricated on chip)
  - Optofluidic ring resonator (capillary based or fabricated on chip)
  - Optical interferometric sensor (Fabry-Perot sensor)

Shopova et al., Anal. Chem. 80, 2232 (2007)
Sun et al., Analyst 135, 165 (2010)
Reddy et al., Lab Chip 12, 901 (2012)
Scholten et al., Lab Chip 14, 3873 (2014)
Kulkarni et al., Nature Commun. 5 3779 (2014)
On-column flow-through vapor sensors (Optical)

Response time: < 1 s
Detection limit: 1-10 pg
Array detection

Reddy et al., Sens. Actuators B 159, 60 (2011); Reddy et al., Lab Chip 12, 901 (2012)
On-column flow-through vapor sensors (Graphene)

Response time: < 0.1 s
Detection limit: 1-10 pg (ppb)
Array detection

Kulkarni et al., Nature Commun. 5 3779 (2014)
Smart 2-D GC
Simple example

1x1 channel 2-D GC

Sample & carrier gas

Guard column

Detector #1

Carrier gas

Thermal injector

Detector #2

1st Column

3-port valve

2nd Column

Pump

(A) 1 2,3 4,5

Detector #1

Detector #2

Signal (a.u.)

2nd retention time (sec)

Time (sec)

(B) 1 3 2

1st retention time (sec)

Center for Wireless Integrated MicroSensing & Systems
Scale up to more channels

1x2 channel 2-D GC

1D column: 2 m long, i.d. = 0.25 mm, RTX-1 coating
2D column: 0.8 m long, i.d. = 0.25 mm, Carbowax coating
Results

Thermal injector turned on/off only 13 times

Very long second-dimensional separation

Liu et al., Anal. Chem. 84, 4214 (2012)
## Analysis

<table>
<thead>
<tr>
<th></th>
<th>Nonane (#12)</th>
<th>Limonene (#15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>t₁</td>
<td>119 s</td>
<td>179 s</td>
</tr>
<tr>
<td>σ₁</td>
<td>4.36 s</td>
<td>4.95 s</td>
</tr>
<tr>
<td>n₁</td>
<td>20</td>
<td>31</td>
</tr>
<tr>
<td>t₂</td>
<td>12.9 s</td>
<td>26.5 s</td>
</tr>
<tr>
<td>σ₂</td>
<td>0.465 s</td>
<td>1.1 s</td>
</tr>
<tr>
<td>n₂</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Total peak capacity (n₁ x n₂)</td>
<td>240</td>
<td>434</td>
</tr>
<tr>
<td>Total analysis time for analyte</td>
<td>200 s</td>
<td>276 s</td>
</tr>
<tr>
<td>Peak capacity production</td>
<td>72/min</td>
<td>94/min</td>
</tr>
</tbody>
</table>

Peak capacity  \[ n = \frac{\sqrt{N}}{4R_s} \ln\left(\frac{t}{t_0}\right) + 1 \]

- N: plate number
- Rs: desired resolution (Rs=1 in the above table)
- t: retention time
- t₀: hold-up time
Temperature ramping

1D column: 2.7 m long, i.d. = 0.25 mm, HP-5 coating. 
Temperature ramping:
Room temperature for 3 min and then heated up to 150 °C at a rate of 20 °C/min

2D column: 0.7 m long, i.d. = 0.25 mm, Carbowax coating. Room temperature

Assay time is much shorter

Liu et al., Anal. Chem. 84, 4214 (2012)
## Analysis

<table>
<thead>
<tr>
<th></th>
<th>Methyl salicylate (#14)</th>
<th>Jasmone (#17)</th>
<th>Caryophyllene (#19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_1$</td>
<td>180 s</td>
<td>640 s</td>
<td>1,079 s</td>
</tr>
<tr>
<td>$\sigma_1$</td>
<td>9.1 s</td>
<td>46.9 s</td>
<td>34 s</td>
</tr>
<tr>
<td>$n_1$</td>
<td>37</td>
<td>36</td>
<td>92</td>
</tr>
<tr>
<td>$t_2$</td>
<td>175 s</td>
<td>72.7 s</td>
<td>50.1 s</td>
</tr>
<tr>
<td>$\sigma_2$</td>
<td>8.8 s</td>
<td>2.3 s</td>
<td>3.9 s</td>
</tr>
<tr>
<td>$n_2$</td>
<td>53</td>
<td>67</td>
<td>25</td>
</tr>
<tr>
<td>Total peak capacity ($n_1 \times n_2$)</td>
<td>1,961</td>
<td>2,412</td>
<td>2,300</td>
</tr>
<tr>
<td>Total analysis time for analyte</td>
<td>410 s</td>
<td>894 s</td>
<td>1,260 s</td>
</tr>
<tr>
<td>Peak capacity production</td>
<td>287/min</td>
<td>162/min</td>
<td>110/min</td>
</tr>
</tbody>
</table>

### Higher peak capacity
### Higher efficiency
Move to μGC system

1x2 channel 2-D μGC

Sample

Six-port valve

Pump C

1st Column

Three-port valve A

Thermal injector A

2nd Column A

Pump A

2nd Detector A

Thermal injector B

2nd Column B

Pump B

2nd Detector B

Different length

1D column: 1 m long, 0.24 mm x 0.15 mm cross section, OV-1 coating

2D column A: 0.5 m long, 0.24 mm x 0.15 mm cross section, OV-215 coating

2D column B: 0.25 m long, 0.24 mm x 0.15 mm cross section, OV-215 coating
Results (Isothermal)

Separation of 31 workplace hazardous volatile organic compounds reported by California Standard Section 01350 Specification

Liu et al., Lab Chip. 13, 818 (2013)
Results
(Temperature ramping)

Analysis time is shortened

Liu et al., Lab Chip. 13, 818 (2013)
Selective detection
(Heart-cutting detection)

1. Good for specific targets
2. Stand-by mode operation

Liu et al., Lab Chip. 13, 818 (2013)
Smart 3-D GC

Analyte 1-9

Flow-through on-column detector

1D separation

2D separation

3D separation

Chen et al., Anal. Chem. DOI: 10.1021/ac401152v (2013)
Setup

1D column: 0.8 m long, i.d. = 0.25 mm, Rtx-5 ms coating
2D column: 1 m long, i.d. = 0.25 mm, Rtx-1 coating
3D column: 3 m long, i.d. = 0.25 mm, SUPELCOWAX-10 coating
Isothermal at room temperature
Flow rate = 6.5 mL/min

Chen et al., Anal. Chem. DOI: 10.1021/ac401152v (2013)
Simple example

Chen et al., Anal. Chem. DOI: 10.1021/ac401152v (2013)
Isothermal separation of 22 analytes

Chen et al., Anal. Chem. DOI: 10.1021/ac401152v (2013)
3-D chromatogram

3-D chromatogram

2-D chromatogram projected from 3-D chromatogram

Chen et al., Anal. Chem. DOI: 10.1021/ac401152v (2013)
Analysis

<table>
<thead>
<tr>
<th></th>
<th>Chlorobenzene (#18)</th>
<th>m-xylene (#22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_1$</td>
<td>65.5 s</td>
<td>91.5 s</td>
</tr>
<tr>
<td>$\sigma_1$</td>
<td>4.5 s</td>
<td>6.4 s</td>
</tr>
<tr>
<td>$n_1$</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>$t_2$</td>
<td>23 s</td>
<td>95 s</td>
</tr>
<tr>
<td>$\sigma_2$</td>
<td>1.46 s</td>
<td>5 s</td>
</tr>
<tr>
<td>$n_2$</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>$t_3$</td>
<td>116 s</td>
<td>64 s</td>
</tr>
<tr>
<td>$\sigma_3$</td>
<td>1.35 s</td>
<td>1.35 s</td>
</tr>
<tr>
<td>$n_3$</td>
<td>76</td>
<td>24</td>
</tr>
<tr>
<td>Total peak capacity ($n_1 \times n_2 \times n_3$)</td>
<td>21,660</td>
<td>12,000</td>
</tr>
<tr>
<td>Total analysis time for analyte</td>
<td>937 s</td>
<td>1,476</td>
</tr>
<tr>
<td>Peak capacity production</td>
<td>1,336/min</td>
<td>488/min</td>
</tr>
</tbody>
</table>

- 3-D starts to show the strength of high-dimension of separation
- With increased number of dimensions, total peak capacity increases
Proposed project

To develop an automated field-deployable multi-channel 3-dimensional micro-gas chromatography device capable of rapid (~20 minutes), sensitive (~ppb to sub-ppb), and *in-situ* analysis of >100 indoor (S)VOCs for human exposure assessment.
Proposed task #1 (Year 1)

1. Microfabrication to reduce the cost and system complexity
2. Modular design for ease of scale-up and re-configuration
Proposed task #1 (Year 1)

1. Simulation to better understand the smart GC design

2. Algorithm for better peak detection

3. Algorithm to more efficiently use analysis time and peak capacity
   How to maximize the total peak capacity while minimizing the assay time
Simulation for smart 1x2x4 channel GC$^3$
(Most recent result)

- Isothermal operation for all 3 dimensions
- 150 VOCs
- Able to separate 94% of 150 VOCs in 6 minutes
Proposed task #2 (Year 2)

System assembly and testing

<table>
<thead>
<tr>
<th>µGC</th>
<th>Weight</th>
<th>Size</th>
<th>Sensitivity</th>
<th>Automation</th>
<th>Total analysis time</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-D</td>
<td>2-3 kg</td>
<td>Desktop</td>
<td>1-10 pg</td>
<td>Yes</td>
<td>&lt;20 min. for 150 VOCs</td>
</tr>
</tbody>
</table>
Proposed task #3 and #4 (Year 3)

3-D GC measurement of 150 (S)VOCs related to indoor environment

20 min analysis time
Quantification of >90% of 150 (S)VOCs
Building a 3-D chromatogram reference library
Benchmarking against standard GC-MS
Acknowledgement

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Global Challenges for a Third Century

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