Drugs, drug precursor and hazardous chemical sensing by quantum cascade laser and cantilever enhanced photoacoustic spectroscopy

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This work is part of the FP7 EU project called CUSTOM - Drugs And PreCursors Sensing By Complementing Low COst Multiple Techniques.

The project has started in 2010 and will last to 2013.

The aim of the project is to build a portable device for drug precursor sensing from vapor phase based on the two orthogonal techniques, which are laser photoacoustic sensor and fluorescence optochip.

In this presentation the development of the cantilever enhanced photoacoustic detector combined with the widely tunable external cavity quantum cascade laser is introduced.
The drug problem is a serious concern all over the world and many attempts to undertake trafficking have been made in the past two decades.

One good way to avoid narcotics traffic is to intercept the drugs before they are shipped into the consuming nations.

However, is even better to stop the fabrication of these illegal substances if possible. These can be achieved controlling the substances used to manufacture the final narcotic drugs and psychotropic substances.

The International Narcotics Control Board (INCB) continues focusing its efforts on preventing the diversion of precursor chemicals used in the illicit manufacture of heroin, cocaine and amphetamine-type stimulants (ATS).

The official reference work for international control of precursors is Article 12 of the 1988 United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances. The Convention establishes two tables listing 23 substances frequently used in the illicit manufacture of narcotic drugs and psychotropic substances, whose diversion to illicit ends should be prevented.
## Drug precursor molecules

### Table I

<table>
<thead>
<tr>
<th>Category 1</th>
<th>CHEMICAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ephedrine</td>
</tr>
<tr>
<td>2</td>
<td>Ergometrine</td>
</tr>
<tr>
<td>3</td>
<td>Ergotamine</td>
</tr>
<tr>
<td>4</td>
<td>Lysergic acid</td>
</tr>
<tr>
<td>5</td>
<td>1-phenyl-2-propanone (BMK)</td>
</tr>
<tr>
<td>6</td>
<td>Psuedoephedrine</td>
</tr>
<tr>
<td>7</td>
<td>N-acetylanthranilic acid</td>
</tr>
<tr>
<td>8</td>
<td>3,4Methylenedioxy -phenylpropan-2-one (PMK)</td>
</tr>
<tr>
<td>9</td>
<td>Isosafrole</td>
</tr>
<tr>
<td>10</td>
<td>Piperonal</td>
</tr>
<tr>
<td>11</td>
<td>Safrole</td>
</tr>
<tr>
<td>12</td>
<td>Norephedrine</td>
</tr>
</tbody>
</table>

### Table II

<table>
<thead>
<tr>
<th>Category 2</th>
<th>CHEMICAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>Acetic anhydride</td>
</tr>
<tr>
<td>14</td>
<td>Potassium permanganate</td>
</tr>
<tr>
<td>15</td>
<td>Anthranilic acid</td>
</tr>
<tr>
<td>16</td>
<td>Phenylacetic acid</td>
</tr>
<tr>
<td>17</td>
<td>Piperidine</td>
</tr>
</tbody>
</table>

### Table III

<table>
<thead>
<tr>
<th>Category 3</th>
<th>CHEMICAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>Acetone</td>
</tr>
<tr>
<td>19</td>
<td>Ethyl ether</td>
</tr>
<tr>
<td>20</td>
<td>Methyl ethyl ketone (MEK)</td>
</tr>
<tr>
<td>21</td>
<td>Toluene</td>
</tr>
<tr>
<td>22</td>
<td>Sulphuric acid</td>
</tr>
<tr>
<td>23</td>
<td>Hydrochloric acid</td>
</tr>
</tbody>
</table>

**Category 1:** indispensable for the manufacture of synthetic drugs  
**Category 2:** important reagents  
**Category 3:** common reagents
Detection system

The portability is achieved by battery operation.
- The Lithium Polymer (LiPo) technology

Gas sampler provides the sample to the **preconcentrator**, FLUO sensor and LPAS sensor. Drug precursor concentrator is used depending on the **operational mode**.

The **LED induced Fluorescence** (FLUO) sensor consists of a light source, a detector at a specific wavelengths, biomolecules and a bifurcated optical fiber system or an optical system based on dichroic mirror.

- **Laser photoacoustic sensor** (LPAS) consists on cantilever enhanced photoacoustic cell and external cavity quantum cascade laser.

- **Blind analyses method**
- **Partial Least Squares - Discriminant Analysis (PLS-DA) method**
- **The final PLS-DA models**

- Mainly on the TouchScreen
- Startup, security access, selecting the operating mode, acquire button, environmental conditions
- Access to the saved data and to the hardware setting parameters for custom operation
Photoacoustic technology with cantilever pressure sensor

- Photoacoustics is proved to be extremely sensitive technique in gas analysis – there is a long tradition of very sensitive measurements with gas lasers.
- Gasera is offering a choice for enhancing the microphone sensitivity by using an optical microphone with a cantilever pressure sensor.
- Cantilever is made out of silicon and has dimensions in the level of: length 5 mm, width 1.2 mm, thickness 10 μm.
- Because the cantilever has very low spring constant (1 N/m), it reacts to extremely low pressure variations.
- The cantilever movement is measured optically with a compact laser interferometer, which allows wide dynamic range for the measurement of movements from below 1 pm to over 10 μm.
Laser photoacoustic module

- Required sensitivity (< 50 ppb) with short measurement time is achieved by using relatively high output power laser (100 mW) in the MID-IR range and highly sensitive cantilever microphone.
- Selectivity is achieved by using widely tunable laser (200 cm\(^{-1}\)), short absorption path, and novel chemometric techniques for spectral interpretation.
The realization of the laser photoacoustic sensor module looks like this.
The dimensions of the module are: width 13 cm, length 30 cm and height 18 cm.
**LPAS Breadboard demonstrator with CW-DFB-QCL**

- The first breadboard demonstrator included a 1353.15 cm\(^{-1}\) CW DFB QC laser and PA201 photoacoustic detector with gas sampling.
- Photoacoustic spectra were measured with methane gas with narrow wavelength band.
- The repeatability data is used for estimating the photoacoustic cell noise in the wavelength selection.
- Modulation studies were made and wavelength modulation, mechanical chopper and electrical modulation were compared.
- The capability of measuring photoacoustic spectra and their correspondence to database spectra was proved.

**Table I. Results of test measurement and estimated noise levels of target molecules in concentration units.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test Setup</th>
<th>Final prototype</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gas</strong></td>
<td>Methane</td>
<td>Acetic anhydride</td>
</tr>
<tr>
<td><strong>Wavenumber [cm(^{-1})]</strong></td>
<td>1353,15</td>
<td>1134</td>
</tr>
<tr>
<td><strong>Laser Power [mW]</strong></td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td><strong>Measurement time per wavenumber [s]</strong></td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Absorbance (1 ppm - meter)</strong></td>
<td>3.4 x 10(^{-4})</td>
<td>2.8 x 10(^{-3})</td>
</tr>
<tr>
<td><strong>PA-cell NNEA</strong></td>
<td>8.9 x 10(^{-10})</td>
<td>8 x 10(^{-10})</td>
</tr>
<tr>
<td><strong>Detection limit – 2 x rms noise level [ppb]</strong></td>
<td>60</td>
<td>0.3</td>
</tr>
</tbody>
</table>
Example measurements were done with continuous wave external cavity quantum cascade laser (CW ECQCL) provided by Dayligth Solutions.

The wavenumber range was between 1020 cm\(^{-1}\) – 1100 cm\(^{-1}\).

Example gases that were measured were: ammonia, methanol and BMK.

The power of the laser at this wavenumber range was between 0 mW - 62 mW.

The photoacoustic cell was Gasera PA201 detector (cell diameter 4 mm, length 100 mm).

Amplitude modulation with mechanical chopper was done.

FFT software was used for selecting amplitude from the modulation frequency – (phase lock would give better results by order of 2)
Example measurement with ammonia – EC-QC laser

- The laser for the measurement was provided by the Dayligth Solutions Inc.
- It was possible to tune the laser wavenumber between $1020 \text{ cm}^{-1} - 1100 \text{ cm}^{-1}$
- This range included several fundamental vibrational absorption lines of ammonia
- The optical output power of the laser was 62 mW at $1068 \text{ cm}^{-1}$.
- Comparison to HITRAN simulation gives a very good match.

Laser output power in the full tuning range

Measured photoacoustic spectrum of ammonia
Example measurement - BMK and methanol

- The measurement was performed by modulating the amplitude mechanically by chopper and tuning the laser wavelength in 0.1 cm⁻¹ steps from 1020 cm⁻¹ to 1100 cm⁻¹. The signal was collected with 0.897 s integration time.

- Comparison to HITRAN model and FTIR measurement was performed indicating a very good match between the line positions and spectrum details.

- Estimated from the signal strength the detection limit for the BMK would be 5 ppb and for methanol 0.2 ppb in 1 s integration time for one spectral point.
FTIR spectra of example target molecules

- Measured quantitative FTIR spectra of target molecules with FTIR instrument and White cell (Acetic anhydride, BMK, Ephedrine).
- These spectra can be used for the comparison to LPAS spectra and for detailed laser wavelength selection.
- Air and polluting molecule spectra were taken from HITRAN and PNNL databases.

Acetic anhydride

BMK

Ephedrine

Spectral range in the test measurement shown
In order to be able to measure ppb level concentrations selectively in an varying environment proper selection of wavelength range is important, for the wavelength selection 7 step procedure was used [1].

STEP 1: Denoising the database spectra by using wavelet transform,
STEP 2: Uniform spectral datasets with constant 1 ppm concentration,
STEP 3: Estimation of the noise structure based on experimental measurements with ECQCL PAS setup,
STEP 4: Design of concentration matrices
- Target mixtures (1 – 4 different target molecules)
- Pollutants (20 gases – 1-3 gases simultaneously)
- Air (9 gases) randomly generated concentrations using lognormal distribution
- Totally 2000 mixture spectra
STEP 5: combining of spectral data with concentration matrices using sigmoidal transfer function preserving baseline.
STEP 6: Creation a smartgrid procedure to avoid noisy spectral range due to small molecules sharp absorption lines.
STEP 7: Selection of optimal wavelength range (200 cm-1) by maximizing the classification efficiency estimated by Partial-least-squares analysis in cross-validation on a moving window.

[1] Poster presentation at “Convegno Nazionale Sensori” conference 2012:
A FEATURE SELECTION STRATEGY FOR THE DEVELOPMENT OF A NEW DRUG SENSING SYSTEM
Alessandro Ulrici1,2, Marco Calderisi1,2, Renato Seeber2,3, Juho Uotila4, Alberto Secchi5, Anna Maria Fiorello5, Massimiliano Dispenza5
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2. Dipartimento di Chimica, Università di Modena e Reggio Emilia, Via Campi 183, 41125 Modena
3. Consorzio INSTM, Via G. Giusti 9, 50121 Firenze
4. Gasera Ltd., Tykistökatu 4, 20520 Turku, Finland
5. Selex-SI, Via Tiburtina, Km 12,400, 00131, Rome, Italy
Selection of measurement wavelengths and range

- Simulation of final mixture and classification efficiency (sensitivity x selectivity) for the four example molecules was done.
- Best range for all molecules was found around 1200 cm$^{-1}$ leading to the best results in crossvalidation.
- This window goes from 1281.5 to 1082.5 cm$^{-1}$ (spectral resolution = 0.5 cm$^{-1}$) and comprises 364 variables (out of a total of 399 variables, because some were pre-deleted with the Smartgrid due to the presence of sharp peaks of interfering molecules).
- Partial least squares analysis will be finally used for analyzing the measured spectrum.

TS – external test set
CV – cross validation
Paretoscaling plus mean centering in data preprocessing
Autoscaling in data preprocessing
Conclusions

Test measurements and simulations gave very promising results for successful drug precursor sensing from vapor phase.

Test measurements with initial prototype can be started with real samples and measurement scenarios.

The system is aiming to:

- Total measurement time of 10 s and 60 s with two different operational modes
- Sensitivity can be further enhanced with preconcentrator,
- Target detection limit for selective measurement of example molecules is 50 ppb.
- Operational modes for fast sensing with high probability of detection and more accurate sensing with low probability of false alarms.
- Allowable amount of false positives can be adjusted in the first mode, when amount of false negatives is minimized,
- In the second mode the amount of false positives is also minimized.

ECQCL and cantilever enhanced photoacoustics is a good match for extremely sensitive and selective gas analysis when combined to effective spectral interpretation algorithms.

The method can be easily applied to different drug and drug precursor target molecules.
Acknowledgements

Thank you for the

CUSTOM FP7 EU project
  Drugs And PreCUrsor Sensing By Complementing Low COst Multiple Techniques

III-V lab for providing the DFB QCL source!
Dayligth Solutions for providing the EC QCL source!
Thank you!