Challenges and New Opportunities in Industrialising Raman Spectroscopy for PAT Applications

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Oxfordshire
England

Outline

- *Raman Method*
- *Current Status (challenges in PAT)*
- *Emerging Technologies (opportunities in PAT)*
  - *Spatially Offset Raman Spectroscopy SORS (deep layered analysis)*
  - *Displaced Raman Spectroscopy (analysis of transparent containers)*
  - *Transmission Raman (bulk analysis)*
- *Conclusions*

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Raman Technique - Overview

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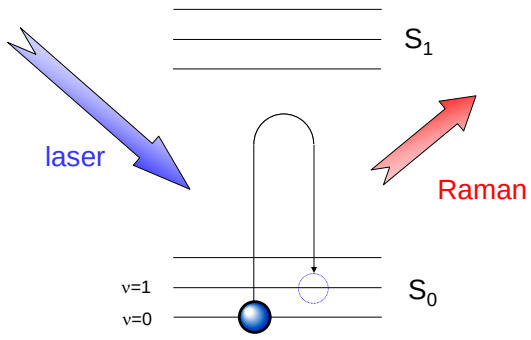

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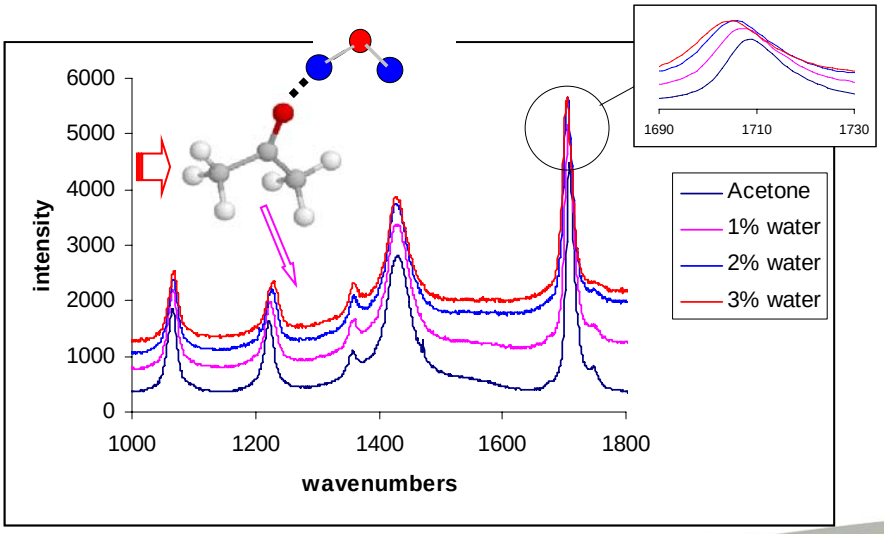
Raman spectrum of acetone with water



Can analyse, for example:

Aqueous samples, slurries, solids, liquids and gases

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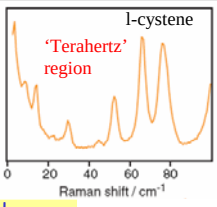
Pro's and Con's of Raman in PAT

Why Raman?

- High chemical specificity
- Compatibility with water
- 'THz region' included as a bonus
- Uses UV/vis/NIR -> good spatial resolution compared with MIR
- Weak process – permits deep probing of materials
- Can be portable
- Can be relatively fast (if not image mapping)
- Can be quantitative

Renishaw's data sheet: NExT



1 THz = 33 cm^{-1}

- Bulk capability (TR) NEW
- Non-invasive deep layer capability (SORS) NEW
- Non-invasive probing of fluorescing containers (DR) NEW
- Medium cost (£10k's)

} with turbid media

Why Not Raman?

- Weak process – not a trace technique (~1%)
- Can be swamped by fluorescence (NIR minimises the issue)

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Examples of Raman Instruments for PAT

Key Requirements/Issues

- Remote data collection (fibres)
- Robust operation in dusty environments
- Compliance with powder explosive environments
- Non-expert operation
- Real-time quantitative feedback
- Fast data collection
- Self calibration
- Safety issues
- Ambient light shielding
- Sample fluorescence

Kaiser's *PhAT System*™ Raman Analyzer for Solids Analysis

Kaiser's RamanRxn3™ PAT Analyzer

Hand-held, battery operated

Renishaw inVia

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Emerging Raman Techniques

Deep Spectroscopy of Powders

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Seeing Invisible

RELEVANT PROBLEM NOT ADDRESSED BY RAMAN UNTIL RECENTLY:

- Deep Non-invasive probing of turbid solids/slurries/liquids
  - In-depth
  - Through thick turbid plastic containers (bottles, capsules, pipes)
- True bulk analysis or tablets/capsules

  - often required in PAT applications

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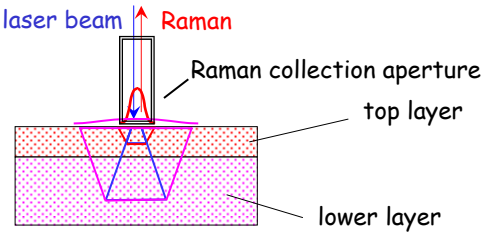
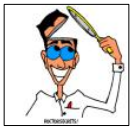
Issues in Deep Raman Spectroscopy in Turbid Media





Conventional confocal Raman microscopy is applicable only to 'shallow' depths in turbid media (~ the photon transport length).

Key issues:

- ❑ Subsurface Raman signal is often overwhelmed by that from the surface layer
- ❑ Mixed up signals – not clear which bottom and which top (unless composition is known *a priory*)

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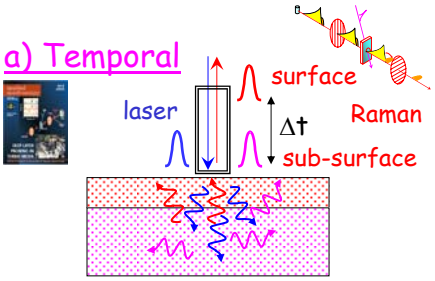
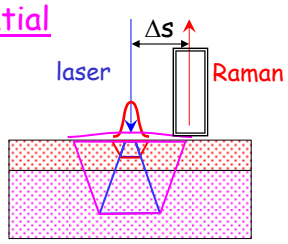
Two Raman Approaches Developed

a) Temporal



Prior Art - used in NIR, fluorescence, single-Raman-band tomography:
- *B.B.Das, Feng Lie, R.R. Alfano, Rep.Prog.Phys.* ***60*** *(1997) 227.*
- *J.Wu, Y.Wang, L.Perelman, I.Itzkan, R.R.Dasari, M. Feld, Appl. Opt.* ***34*** *(1995) 3425.*
- *N.Everall, T.Hahn, P.Matousek, A.W.Parker, M.Towrie, Applied Spectroscopy 55 (2001) 1701.*

b) Spatial



Prior Art - used in NIR, fluorescence:
- *B.B.Das, Feng Lie, R.R. Alfano, Rep.Prog.Phys. 60 (1997) 227.*
- *T.J.Pfefer, K.T.Schomacker, M.N.Ediger, N.S.Nishioka, Appl. Opt.* ***41*** *(2002) 4712.*

- ❑ The variation of Δt or Δs leads to the variation of relative Raman intensities. Higher values lead to the diminishment of surface signal (Raman/fluorescence).
- ❑ This change can be used by PCA to extract pure Raman spectra of layers.

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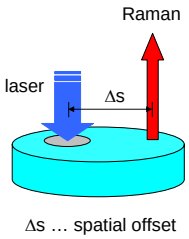
Spatially Offset Raman Spectroscopy (SORS)



Δs … spatial offset

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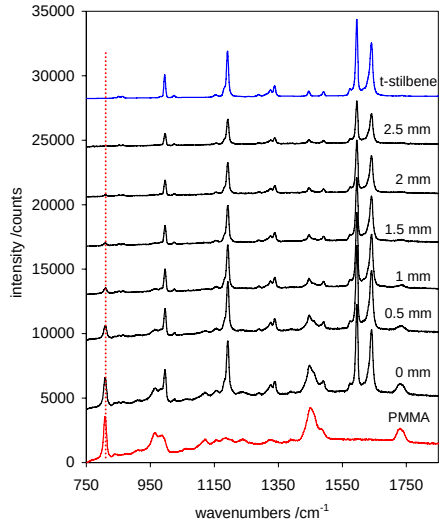
Results

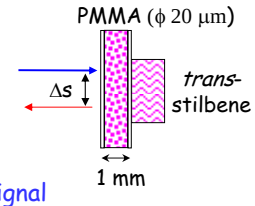


subsurface

subsurface signal

conventional Raman

surface



λ = 514 nm

P. Matousek, I. P. Clark, E. R. C. Draper, M. D. Morris, A. E. Goodship, N. Everall, M. Towrie, W. F. Finney and A. W. Parker, *Appl. Spectrosc.* **59** (2005) 393.

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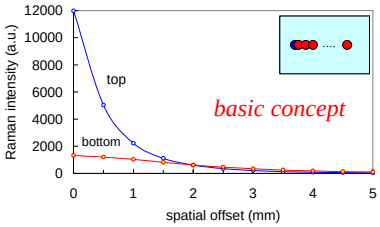
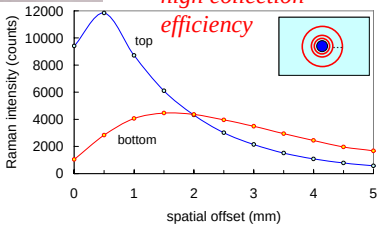
SORS Variants

Point collection

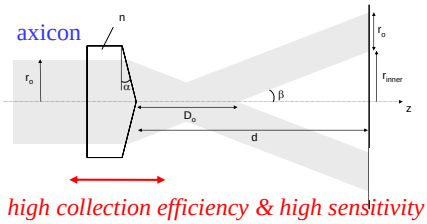


Circular collection

high collection efficiency



Inverse SORS



high collection efficiency & high sensitivity

Axicon

J.H. McLeod, *J. Opt. Soc. Am.* **44**, 592 (1954)
B. Depret, P. Verkerk and D. Hennequin, *Opt. Commun.* **211**, 31 (2002).

Inverse SORS

M.V. Schulmerich, K.A. Dooley, M.D. Morris, T.M. Vanasse, S.A. Goldstein, *J. Biomed. Optics* **11**, 060502 (2006).
P. Matousek, *Applied Spectroscopy* **60**, 1341 (2006).

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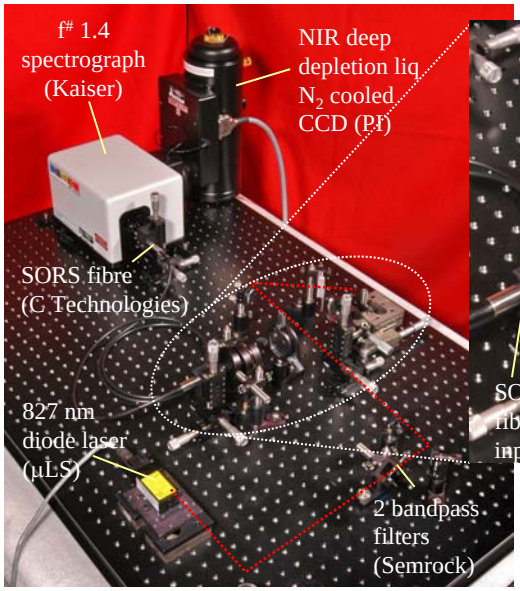
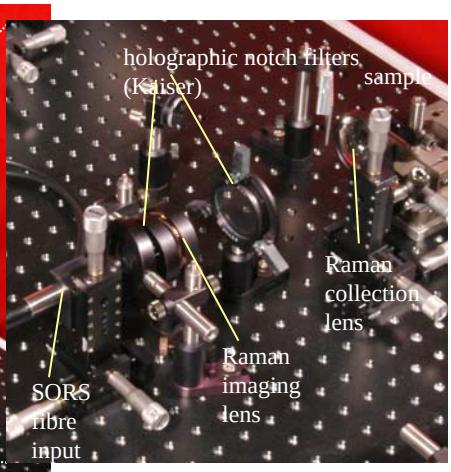
SORS Instrumental Setup





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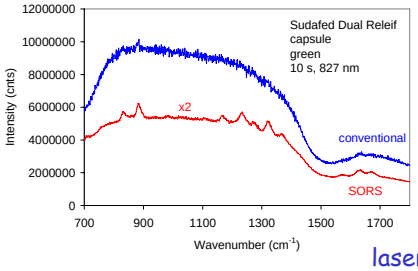
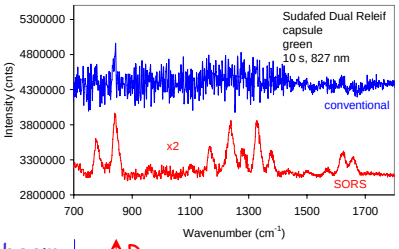
SORS Probing of Pharmaceutical Capsules

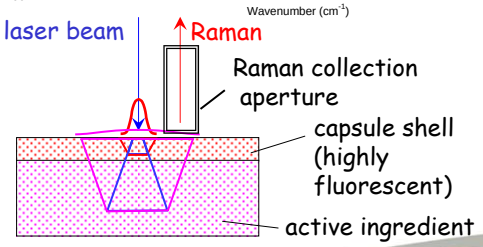
SORS

Raw spectra



Backgrounds removed





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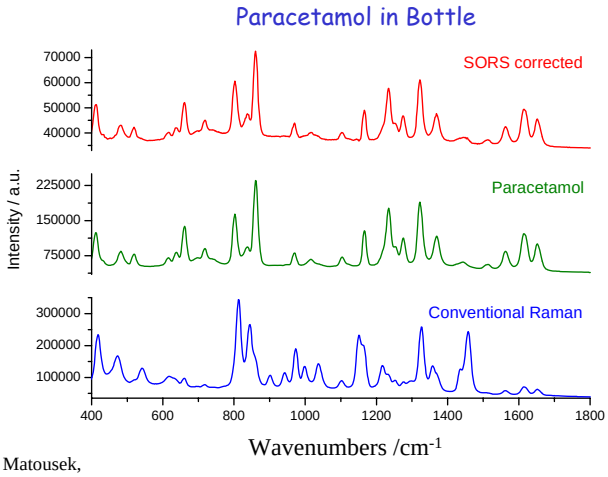
Counterfeit Applications

Counterfeit drugs issue:
• R. Mukhopadhyay, *Analytical Chemistry* 79, 7, 2622 (2007)

SORS



1 s

C. Eliasson, P. Matousek,
Analytical Chemistry **79** (2007) 1696.

Anti-malaria tablets: C. Ricci, C. Eliasson, N. A. Macleod, P. Newton, P. Matousek and S. G. Kazarian, *Analytical and Bioanalytical Chemistry*, in press 2007.

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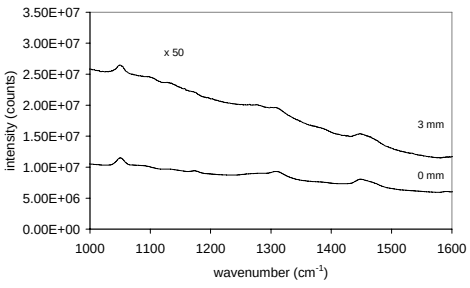
Seeing Through Paint

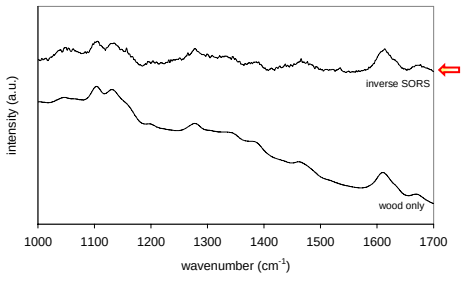
Inverse SORS

Painted wooden block

Raw Spectra



Recovered Spectrum



Adhesion of paint/biofilms to substrates, rust detection, …

P. Matousek, *Applied Spectroscopy* **60** (2006) 1341.

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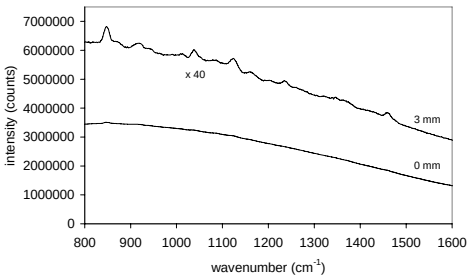
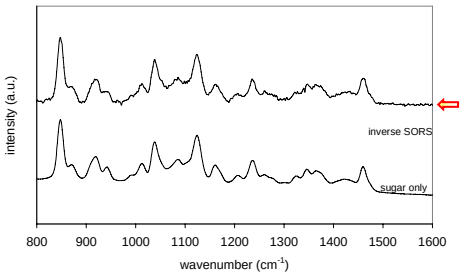
Detection of Powders in Envelopes

Inverse SORS

Raw Spectra



Recovered Spectrum



Security screening

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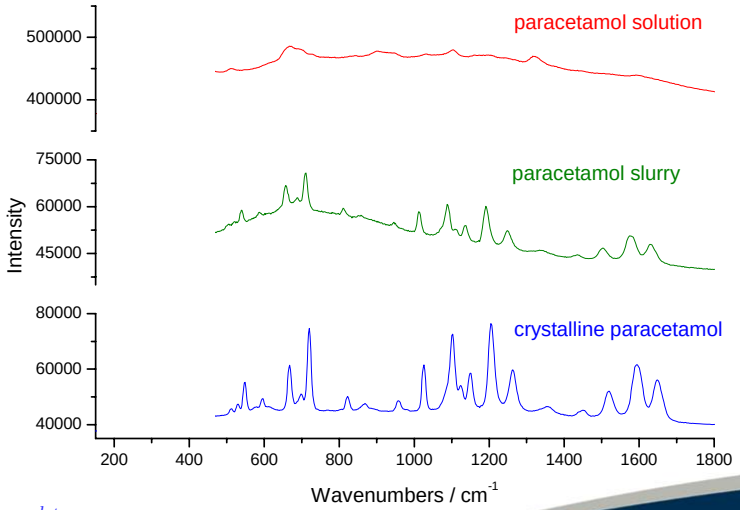
Slurries in PAT Applications



Preliminary data

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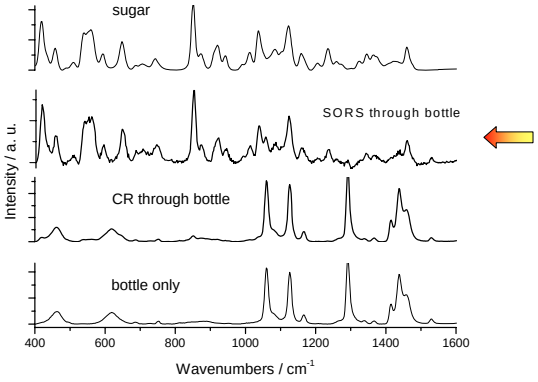
Detection of Powders in Plastic Translucent Containers



1 s

e.g. illicit drugs or powder explosives

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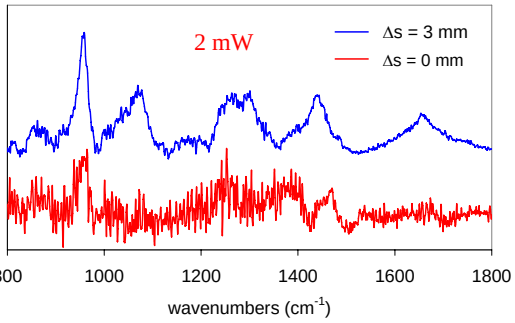
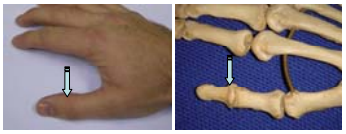
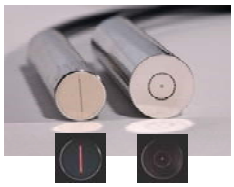
Human Bone Through Skin *In Vivo*

human bone through 2 mm of skin (thumb) in vivo (200 s) at safe levels



SORS
circular collection





λ = 827 nm

P. Matousek, E.R.C. Draper, A.E. Goodship, I.P. Clark, K. Ronayne, A.W.Parker, *Applied Spectroscopy* **60** (2006) 758.

Similar research is also performed by a group of Professor Michael Morris (University of Michigan): M.V. Schulmerich, K.A. Dooley, T.M. Vanasse, S.A. Goldstein and M.D. Morris, *Appl. Spectrosc.* **61**, (2007) 671.

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Displaced Raman Approach (DR)

A hybrid between SORS and conventional Raman
'One geometry for all uses'

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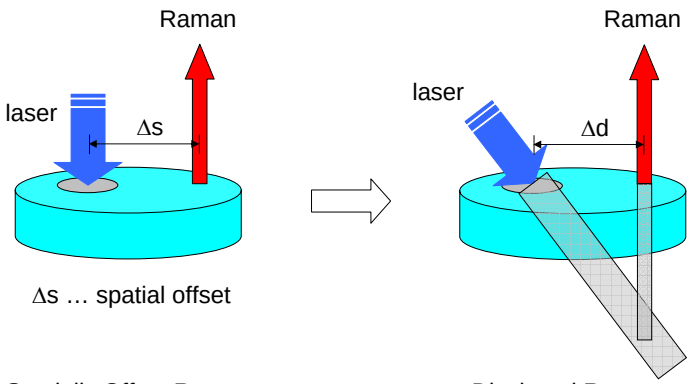
Displaced Raman Concept



Spatially Offset Raman Spectroscopy (SORS)

For diffusely scattering samples

Displaced Raman Spectroscopy

For transparent samples
REDUCES fouling problem or window fluorescence

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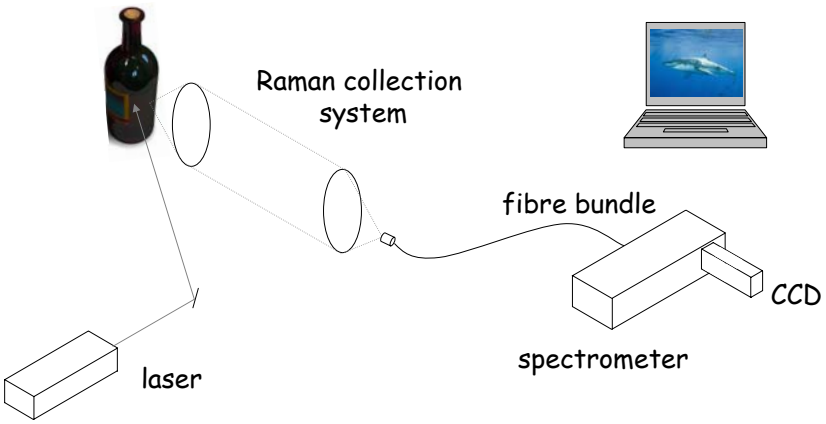
Displaced Raman Deployment



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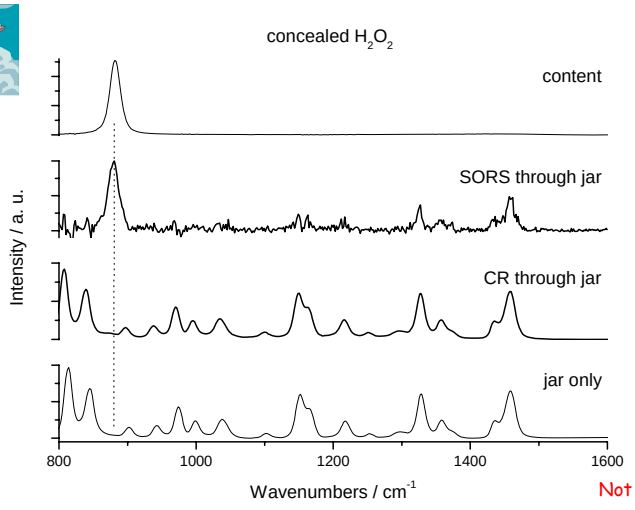
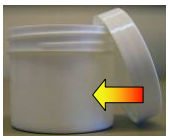
Detection of Liquids Through Bottles



Displaced Raman



1 s

e.g. liquid explosives

Not applicable to metals

C. Eliasson, N.A. Macleod, P. Matousek, Non-invasive Detection of Concealed Liquid Explosives using Raman Spectroscopy, *Anal. Chem.*, in press, 2007.

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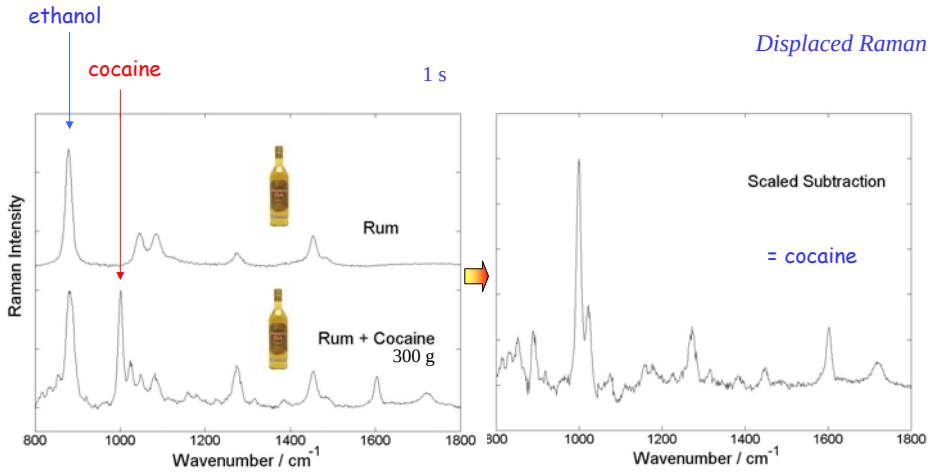
Non-invasive Detection of Cocaine Dissolved in Rum



in collaboration with UK's Government Department

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Bulk Probing of Solids (Transmission Raman)

Elimination of the sub-sampling problem

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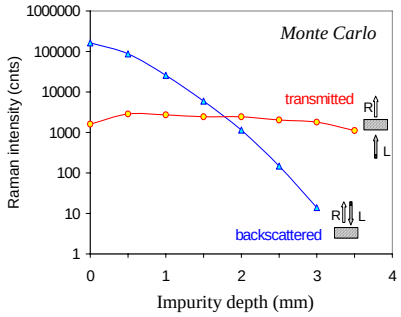
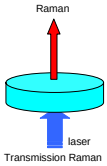
Transmission Raman





Key benefit: Elimination of the sub-sampling problem
P. Matousek, A.W. Parker, *Applied Spectroscopy* **60** (2006) 1353.

Prior Art:

First use of transmission geometry
B. Schrader, G. Bergmann, Fresenius. *Z. Anal. Chem.* **225**, 230 (1967)

Sub-sampling problem of conventional backscattering geometry discussed
H. Wang, C.K. Mann, T.J. Vickers, *Appl. Spectrosc.* ***56***, 1538 (2002).
J. Johansson, S. Pettersson, S. Folestad,
J. Pharnaceutical and Biomedical Analysis **39**, 516 (2005).

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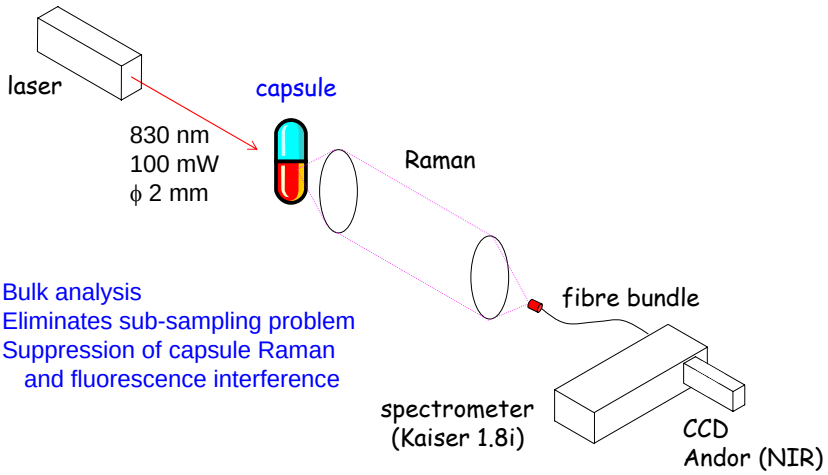
Transmission Raman Spectroscopy



- Bulk analysis
- Eliminates sub-sampling problem
- Suppression of capsule Raman and fluorescence interference

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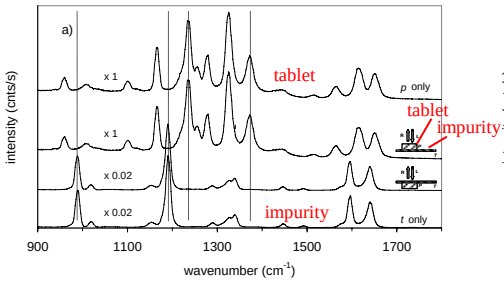
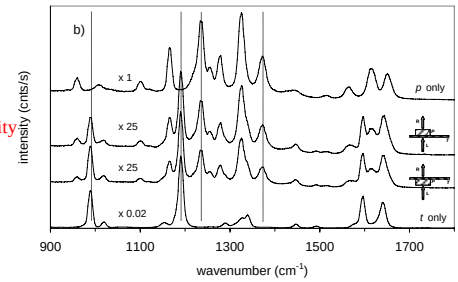
Bulk Tablet Characterisation

Conventional backscattering

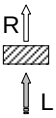


Only surface layer is visible

Transmission



The impurity layer is visible at any location



Elimination of sub-sampling problem!

P. Matousek, A.W. Parker, *Applied Spectroscopy* **60** (2006) 1353.

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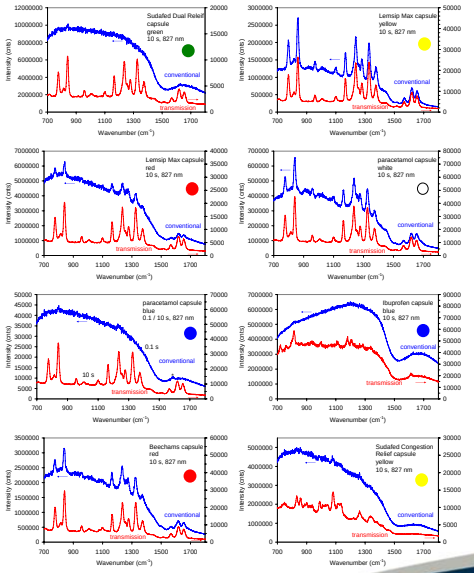
Non-invasive Probing of Coloured Capsules

Transmission Raman

Raw spectra!

Capsule Fluorescence Signal Suppressed



λ = 827 nm
80 mW
10 s

P. Matousek, A.W. Parker,
Journal of Raman Spectroscopy **38** (2007) 563.

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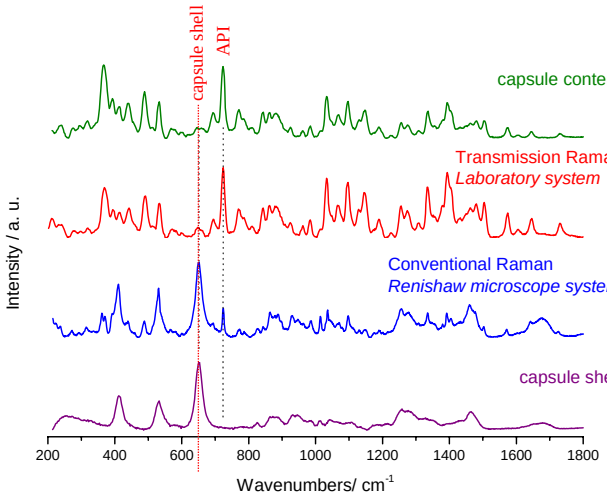
Quantification of Capsule Content using Transmission Raman



Capsule Raman Signal Suppressed (x33)

5 s

In collaboration with Pfizer
(L. Jayes, F. Clarke, S. Hammond, M.R. Smith)

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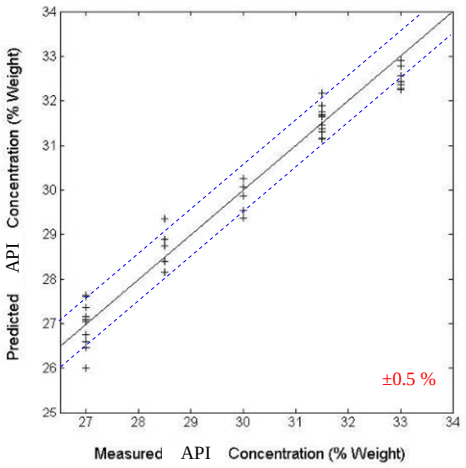
Quantification of Capsule Content using Transmission Raman

API

PLS analysis

Transmission Raman



5 s

In collaboration with Pfizer
(L. Jayes, F. Clarke, S. Hammond, M.R. Smith)

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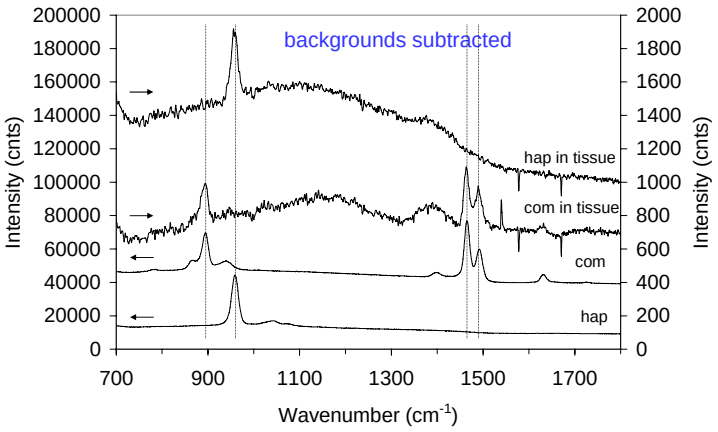
Calcified Material
(chicken breast tissue - 16 mm thick)



Transmission Raman

λ = 827 nm
60 mW
100 s

hap … calcium hydroxyapatite
com …calcium oxalate monohydrate

P. Matousek, N. Stone,
Journal of Biomedical Optics **12** (2007) 024007.

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Passive Boosting of Raman Signals for Higher Sensitivity & Shorter Acquisition Times

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Issues in Deep Spectroscopy

Penetration Depth and Sensitivity are Typically Noise Limited.

In most applications involving deep layer probing weak Raman signals are present with noise limiting the sensitivity and penetration depth.

For maximum sensitivity and penetration depth it is desirable to improve S/N which can be accomplished by enhancing Raman signals.

Adjustable parameters
- eg acquisition time
- laser power
- collection efficiency (Kathryn Dooley, Talk #381, Wednesday)
- by other means ?????

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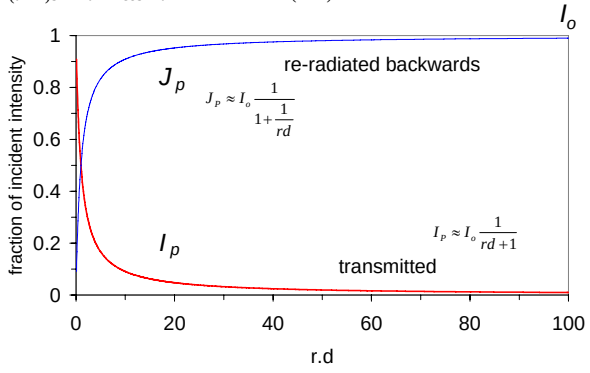
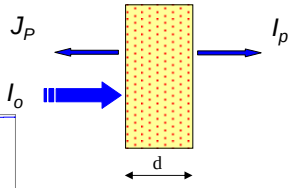
Problem of Coupling Laser Radiation into Turbid Medium

Loss of radiation at the coupling interface

$$I_p = I_o \frac{k}{(a+r)\sinh kd + k\cosh kd} \qquad J_p = I_o \frac{r\sinh kd}{(a+r)\sinh kd + k\cosh kd}$$





r … scattering coefficient

P. Kubelka, F. Munk, *Z. Tech. Phys.* **12**, 593-601 (1931).
B. Schrader, G. Bergmann, Fresenius. *Z. Anal. Chem.* **225** (1967) 230.

Reflective enclosure solution:
B. Schrader, G. Bergmann, Fresenius. *Z. Anal. Chem.* **225** (1967) 230.
J.C. Henderson, Q. Su, R. Grobe, *Laser Physics* **14** (2004) 515.

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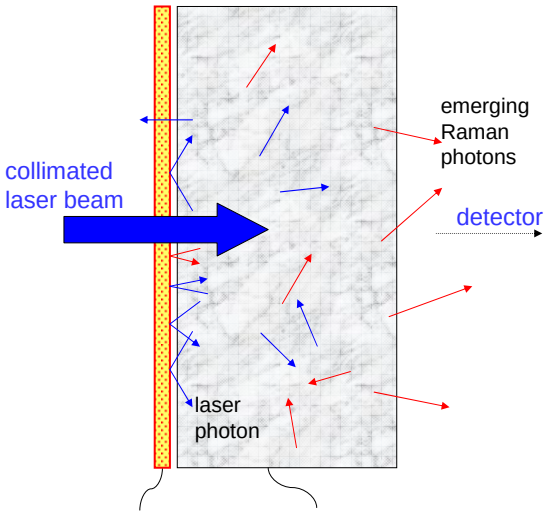
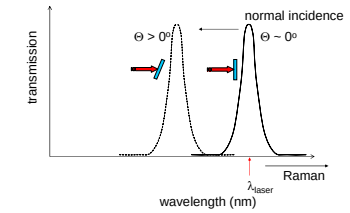
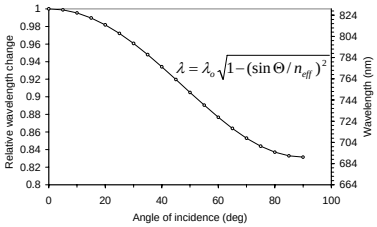
Solution – 'Unidirectional' Mirror

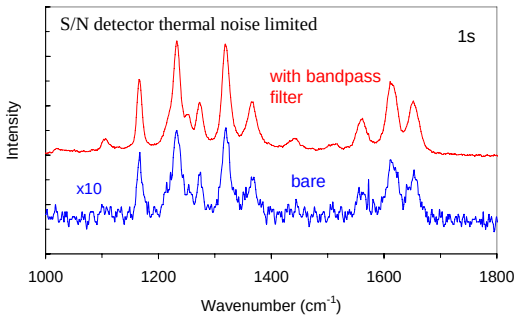


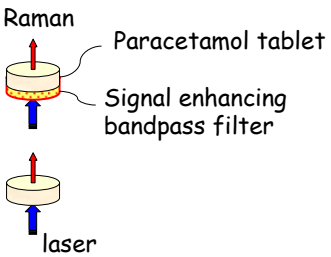


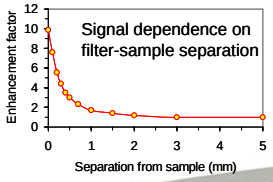


S/N Improvement with Medium Performance Raman Systems

Transmission Raman
Paracetamol tablet (3.9 mm thick)







S/N improvement ~ enhancement factor ~ 10 !
(equivalent to 100-times longer acquisition time)

250 mW
830 nm
1 s
Ocean Optics QE65000
t = -15 °C

P. Matousek, *Applied Spectroscopy* **61** (2007) 845.

Conclusions

Raman

- Coming out of age: A robust, simple method.
- Compatible with PAT goals (enables process monitoring and understanding)
- Software/instrumentation development – eliminates need for specialist
- Adapted for production environment (e.g. Kaiser)
- Cost reduced over the last decade from several $100,000's to $10,000's

New Emerging Technology Removes Key Limitations of Raman

- SORS Non-invasive probing through plastic diffusely scattering (translucent) containers – pipes/bottles – SORS
- DR Combines the benefits of SORS with conventional Raman for probing transparent bottles enabling surface fluorescence rejection
- TR Bulk quantitative analysis (removes the subsampling problem) – (potential to displace NIR in some applications)

Further reading:

P. Matousek, *Chem. Soc. Rev.* **36** (2007) 1292.

http://www.clf.rl.ac.uk/Facilities/LSF/SORS/home.htm

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