Karlsruhe Institute of Technology

At the intersection of microengineering and magnetic resonance: challenges and opportunities

Prof. Dr. Jürgen J. Brandner: juergen.brandner@kit.edu
Dr. Mazin Jouda, Dr. Vlad Badilita, Dr. Sören Lehmkuhl, Dr. Neil MacKinnon

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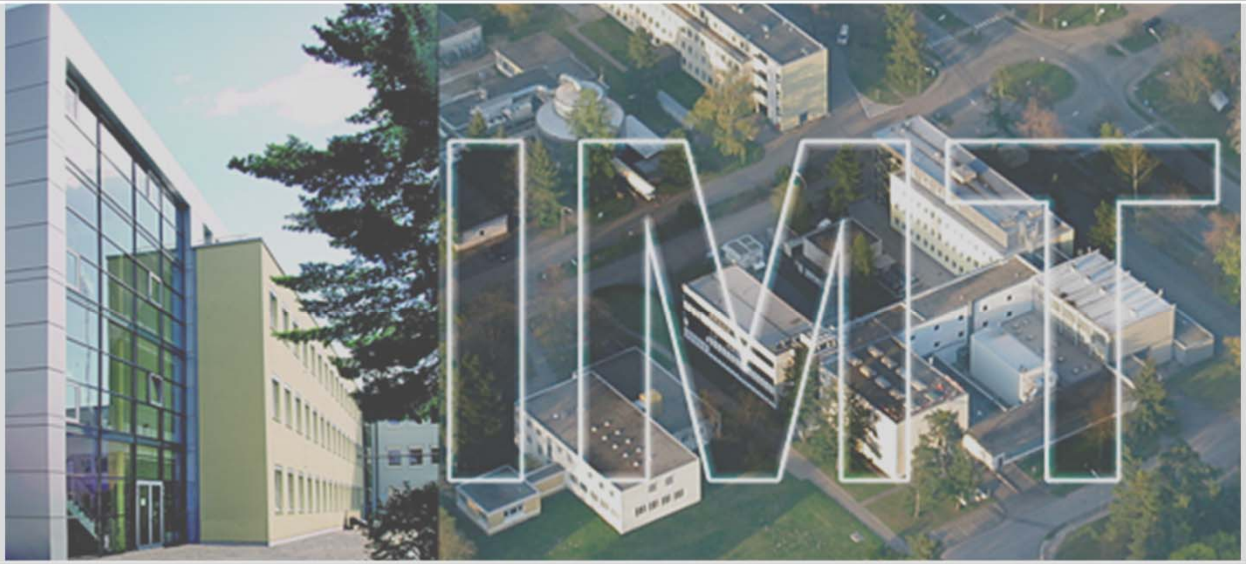
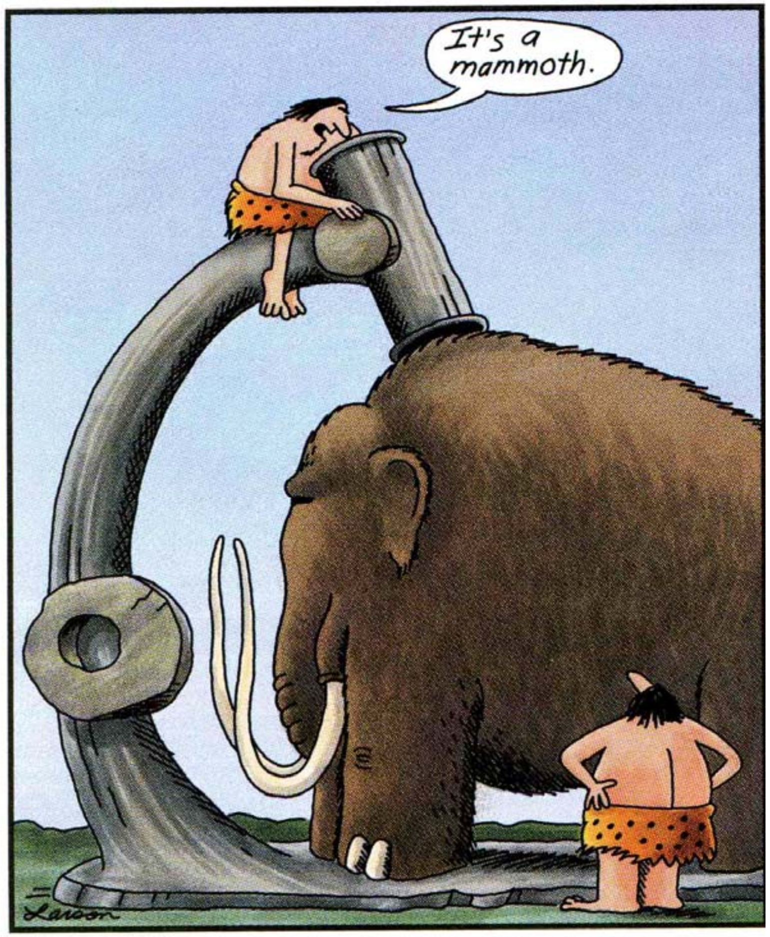


Applications

Content: NMR as measurement tool…

- Microsystems: Miniaturization, Pro’s & Con’s
- (Process) Measurement in Microsystems
  - What measurements needed?
  - Miniaturization and problems with sensors in miniaturized systems.
- Process Measurement Examples, and can *NMR* / *MRI* help?
  - How does it work…
  - Thermal Process Engineering, Ranges
  - Chemical Process Engineering, Ranges
  - Limitations
  - What can be measured by NMR?
  - Visualization
- Summary
  - NMR Pro’s & Con’s



Early microscope

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Measurement means…

- To look as close as possible and necessary…
  …and sometimes with “strange methods”…

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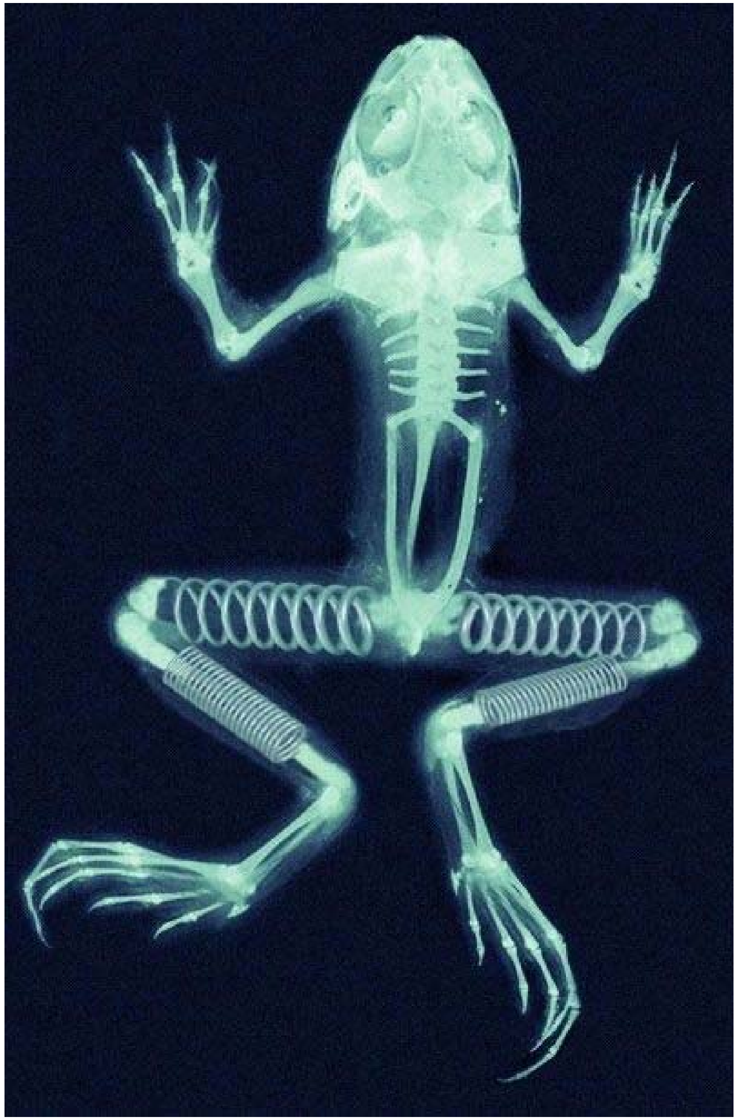
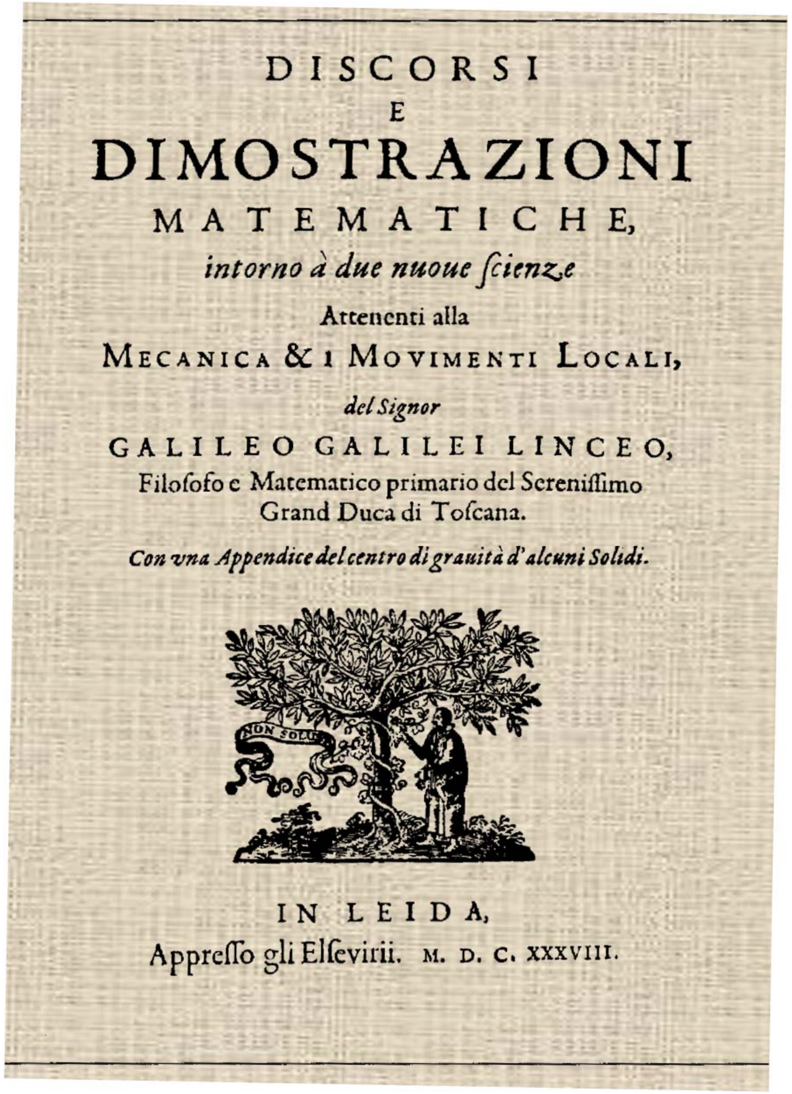
Measuements and what can be found…



Miniaturization by downscaling…

One of the first
publications about scaling:

1638


DISCORSI
E
DIMOSTRAZIONI
MATEMATICHE,
intorno à due nuoue ſcienze
Attenenti alla
MECANICA & I MOVIMENTI LOCALI,
del Signor
GALILEO GALILEI LINCEO,
Filoſofo e Matematico primario del Sereniſſimo
Grand Duca di Toſcana.
Con vna Appendice del centro di grauità d'alcuni Solidi.

IN LEIDA,
Appreſſo gli Elſevirii. M. D. C. XXXVIII.

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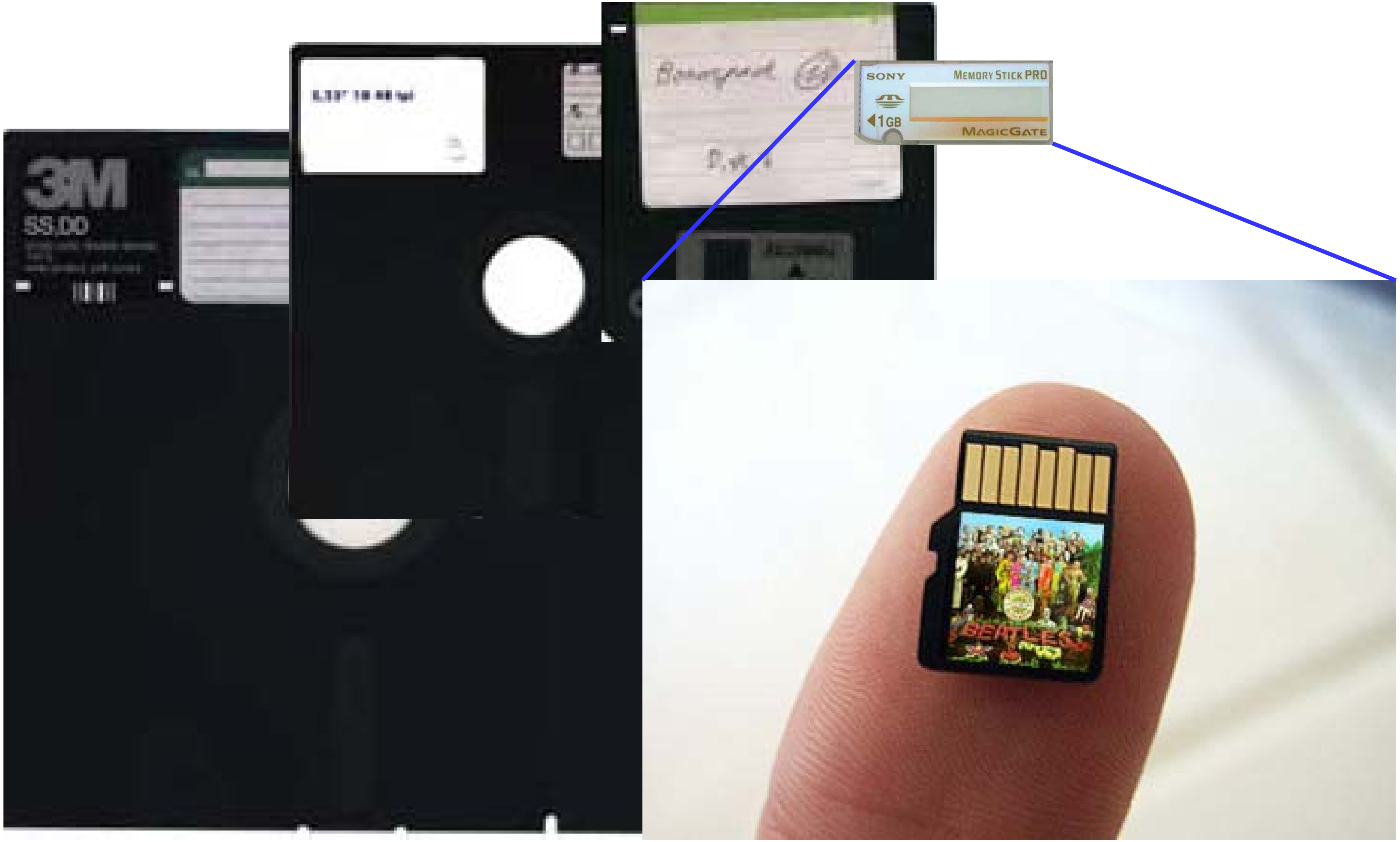
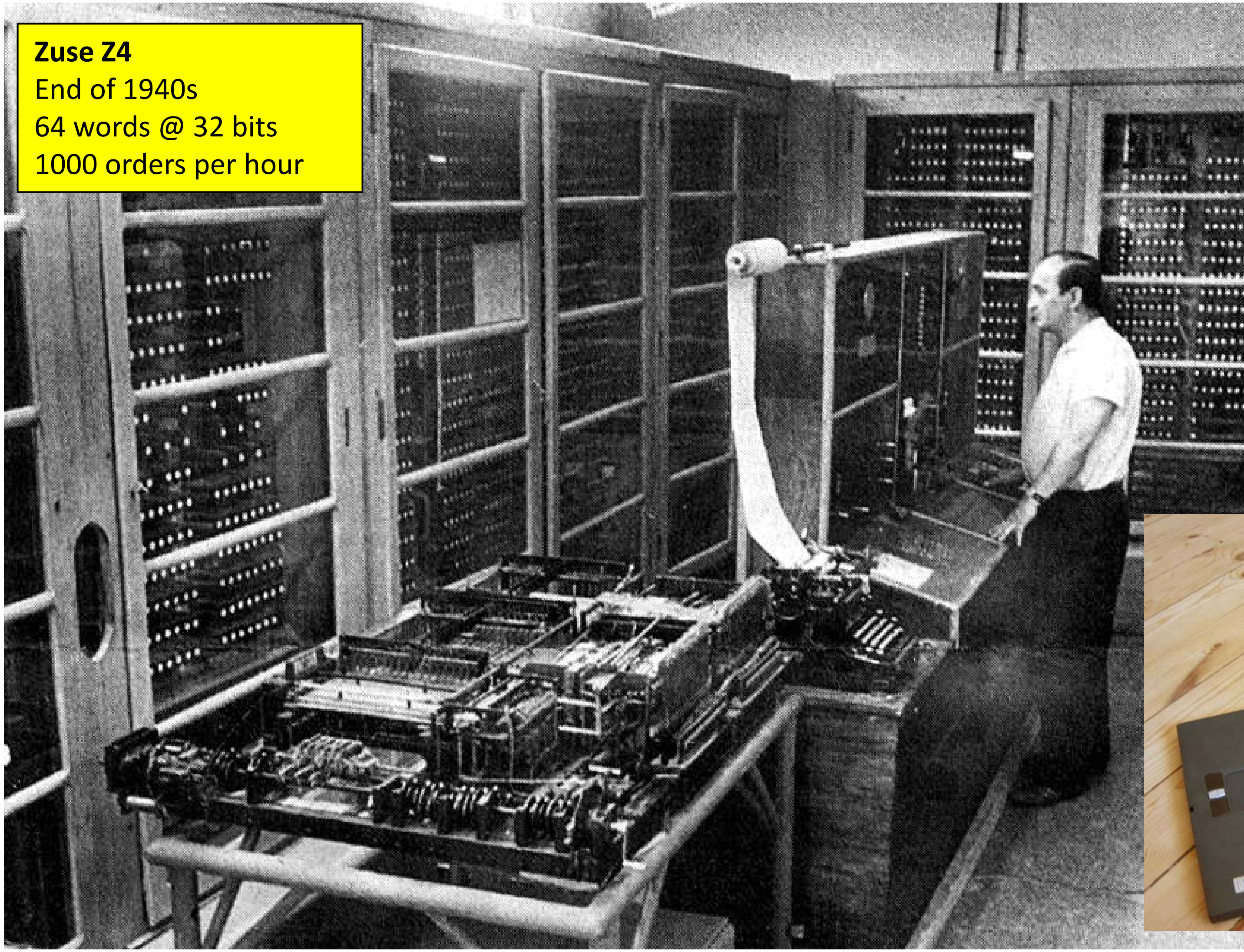
Process Intensification & Miniaturization



Process Intensification & Miniaturization



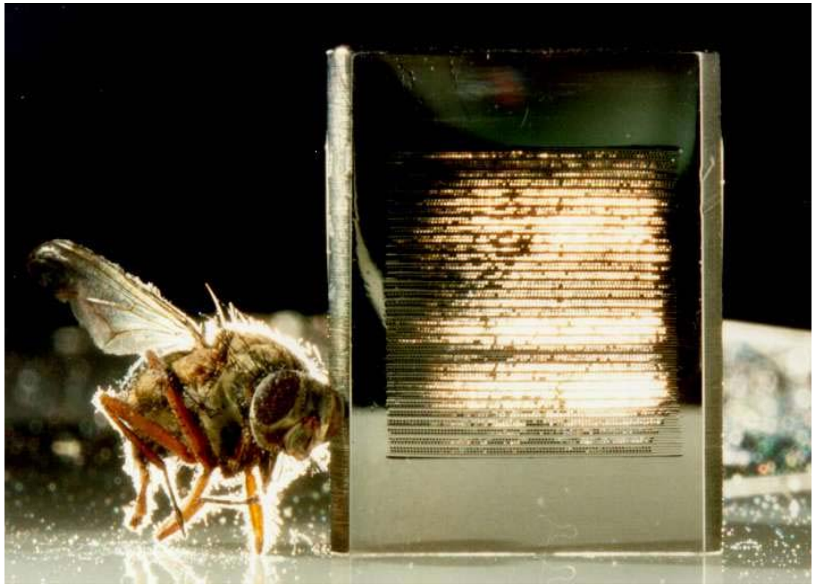
Process Intensification & Miniaturization

Process Intensification & Miniaturization

Process Engineering Micro Equipment

Micro System

A system, in which the dimensions of parts being relevant for the functionality are below 1mm can be named a micro system.



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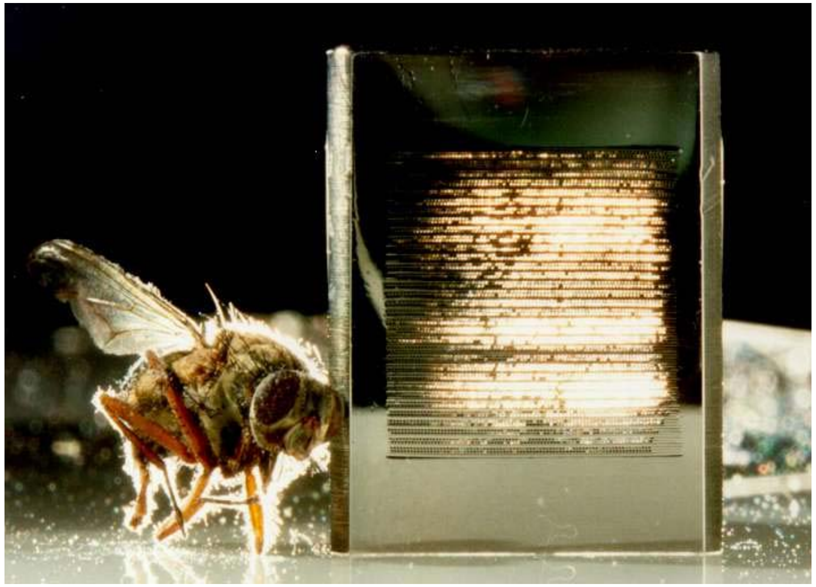
Process Engineering Micro Equipment

Micro System

A system, in which the dimensions of the active fluid flows are small enough to overcome limitations can be named a micro system for process engineering.



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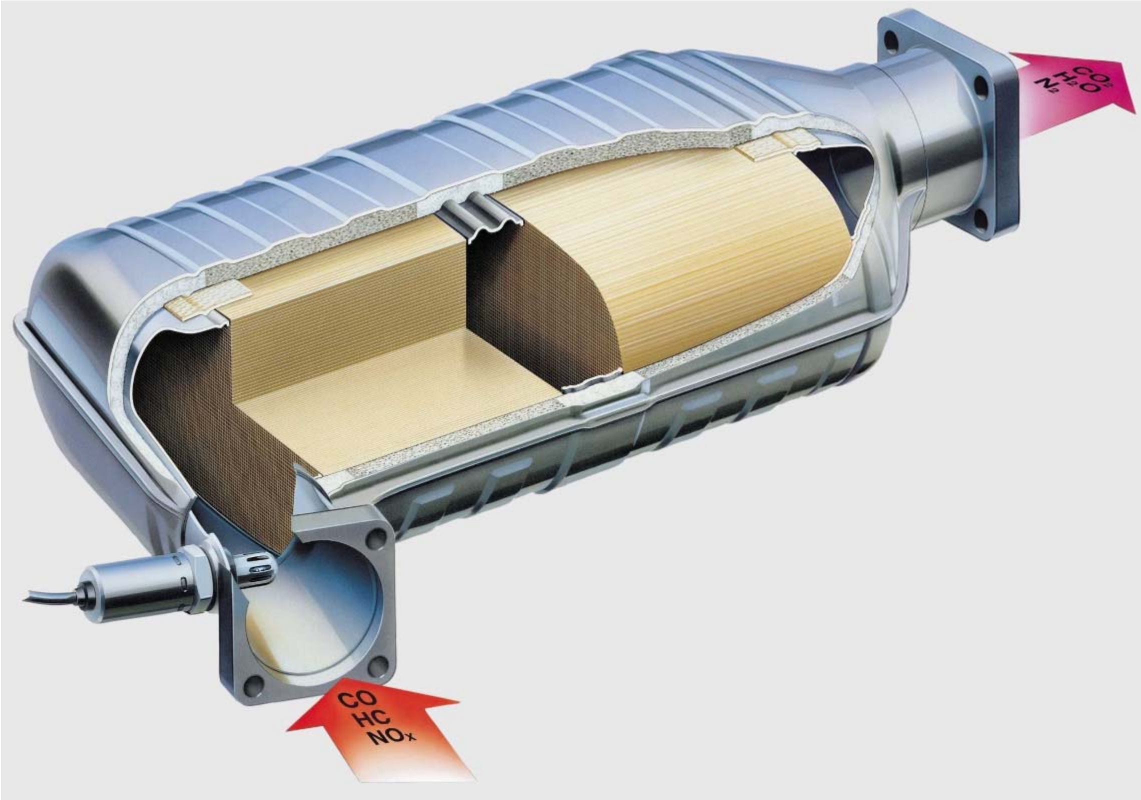
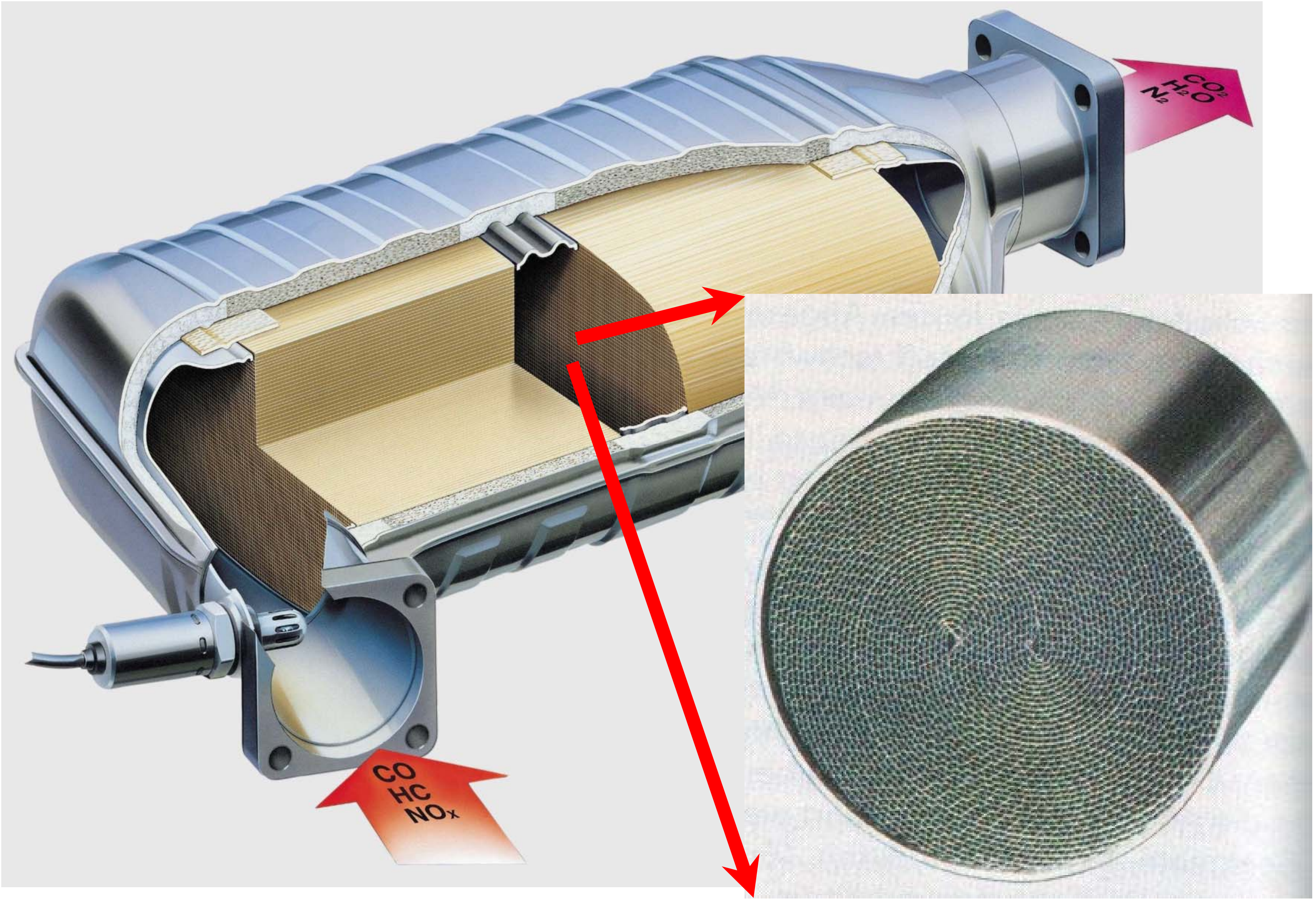
Processes in Miniaturized Equipment

Process Engineering in Miniaturized Equipment means to perform *chemical/physical/physico-chemical/bio-medical processes with microstructured devices.*

Most common example: Automotive exhaust gas catalyst

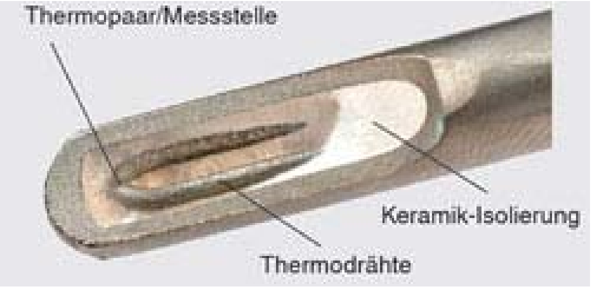


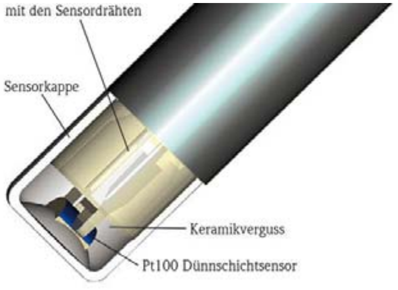
Processes in Miniaturized Equipment



Process Measurements

- In general: All parameters to describe the (mechanical) flow behavior / thermal behavior / mass transfer behavior / (bio-)chemical behavior in the most comprehensive way.
- For many of those parameters, measurement solutions for macroscopic systems are existing and well established.
  - Simple examples:
    - Temperature sensors for fluid temperature measurement.





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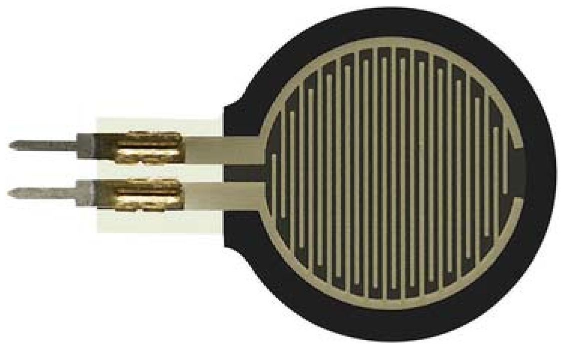
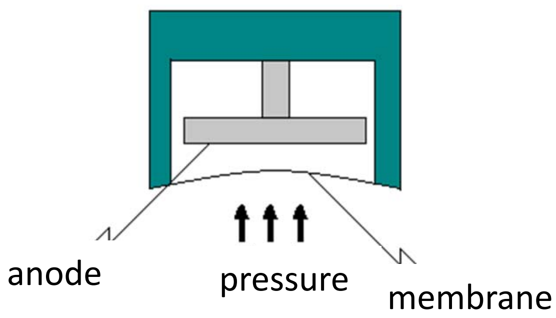
    - Temperature sensors for fluid temperature measurement.
    - Pressure sensors for system pressure measurement.





The Micro Measurement Problem

- If it's too large…

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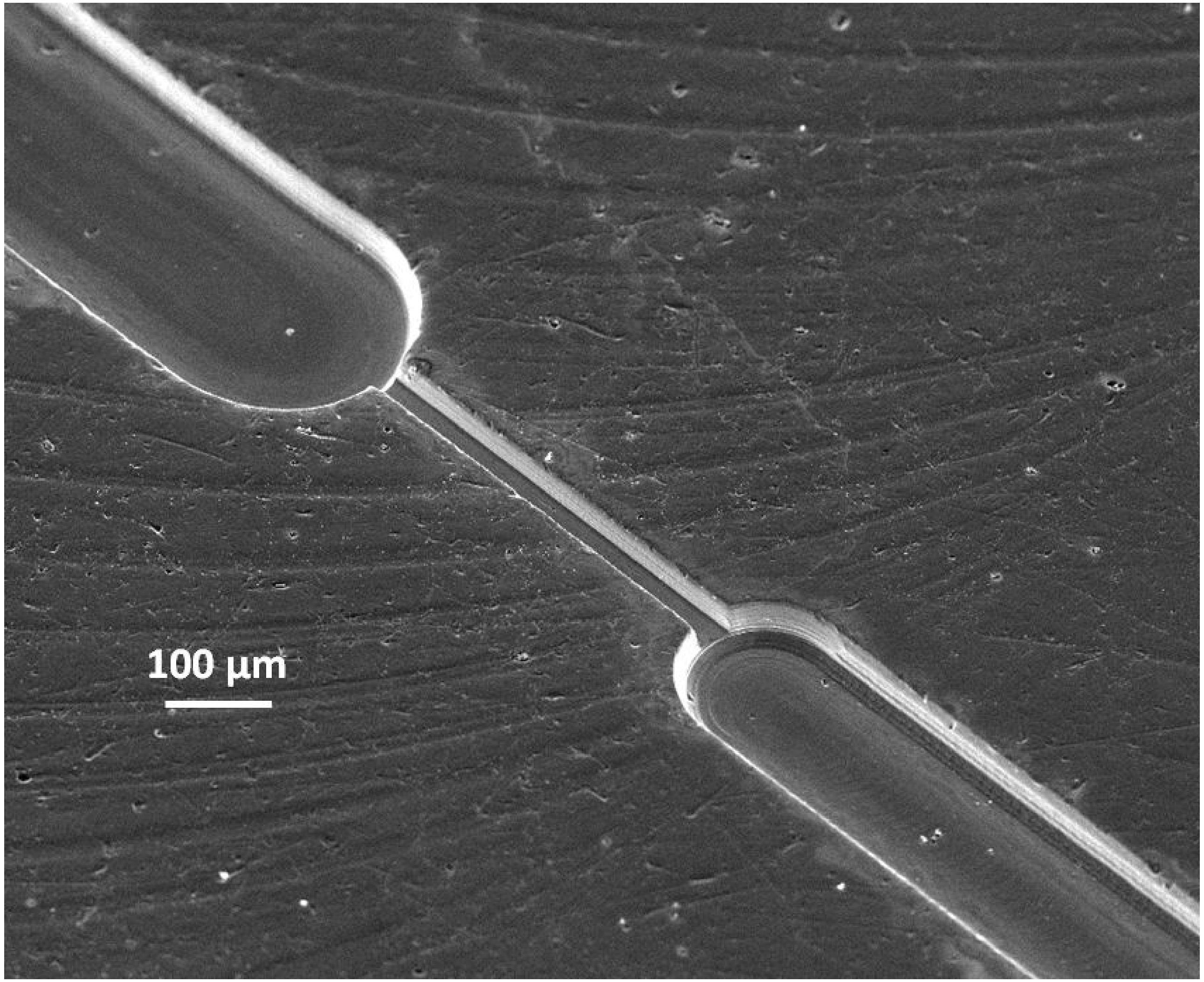
The Micro Measurement Problem

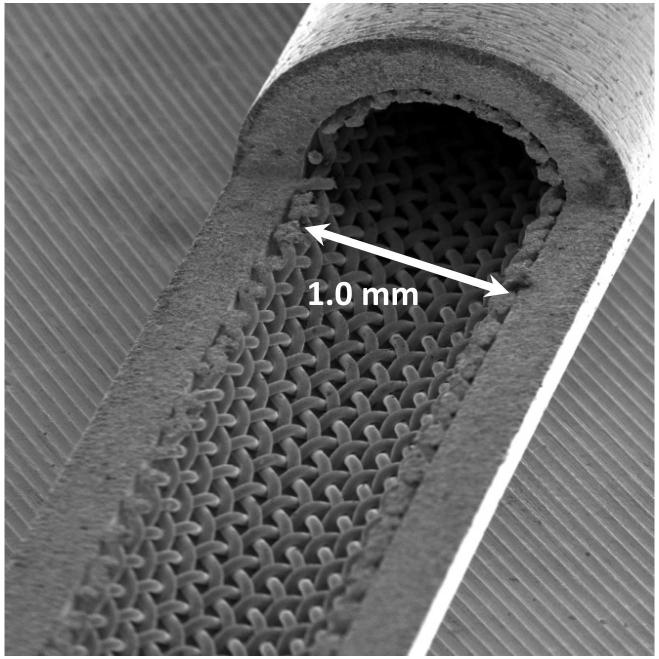
- If it's too large…

The Micro Measurement Problem

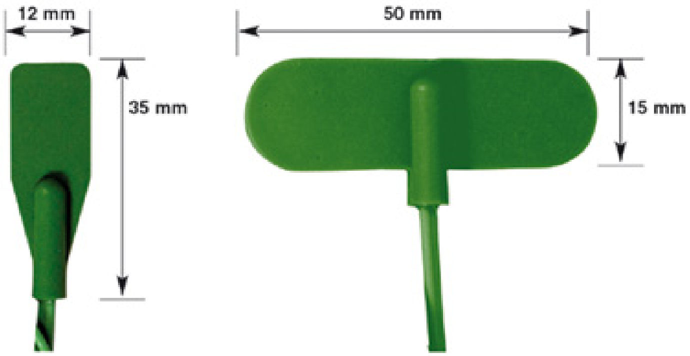


The Micro Measurement Problem

- Dimensions of the sensor often in the same range than those of the most considerable dimension of the microsystem.
  - Example: Hydraulic diameter of flow channels



Micro Heat Pipe



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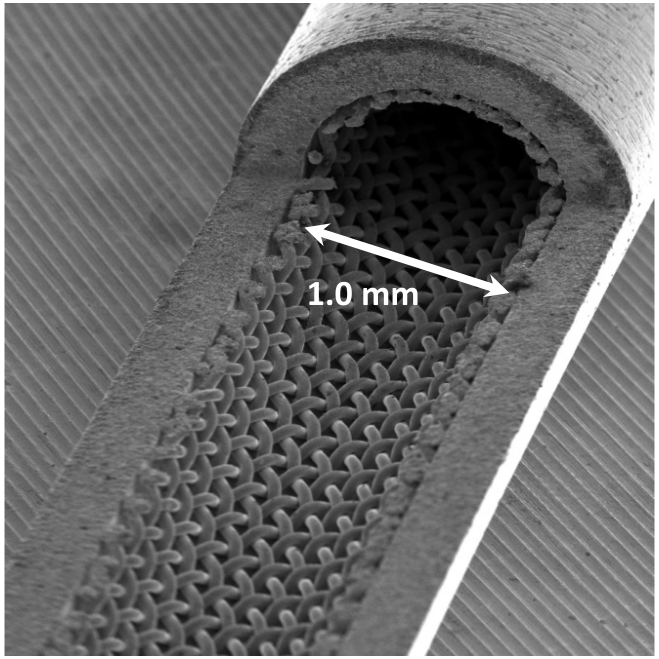

Micro Heat Pipe

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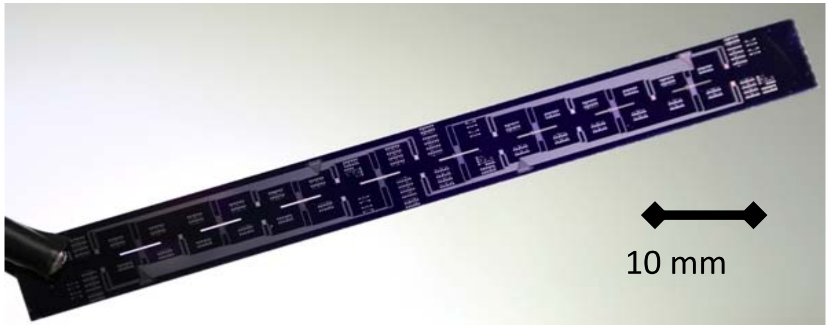
Process Measurements in Microsystems

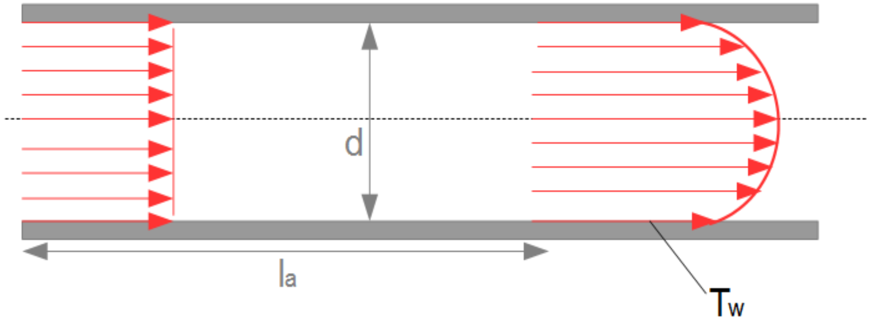
- Dimensions of the sensor often in the same range than those of the most considerable dimension of the microsystem.
- In this case: fluidic / temperature / reactive (etc) behavior is largely influenced by the sensor or sensor makes it impossible to measure!
- Measuring at the boundary layer / wall is not sufficient!

Silicon chip with miniaturized thermopiles (differential temperature measurement) and RTDs (reference temperature).



Laminar temperature start

Fully developed laminar temperature profile

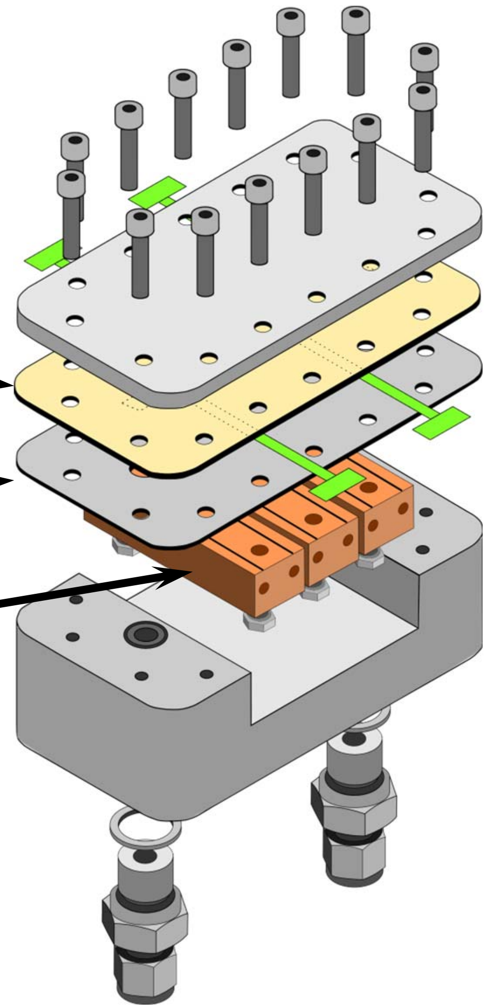


Process Measurements in Microsystems

- Microstructure devices to measure with such sensors become rapidly very complex!

  Multilayer design

  - Sensor chip integrated on PTFE layer as channel top wall
  - Exchangeable test sections with a single microchannel open on top
  - Heating/cooling unit with three separately controlled copper blocks



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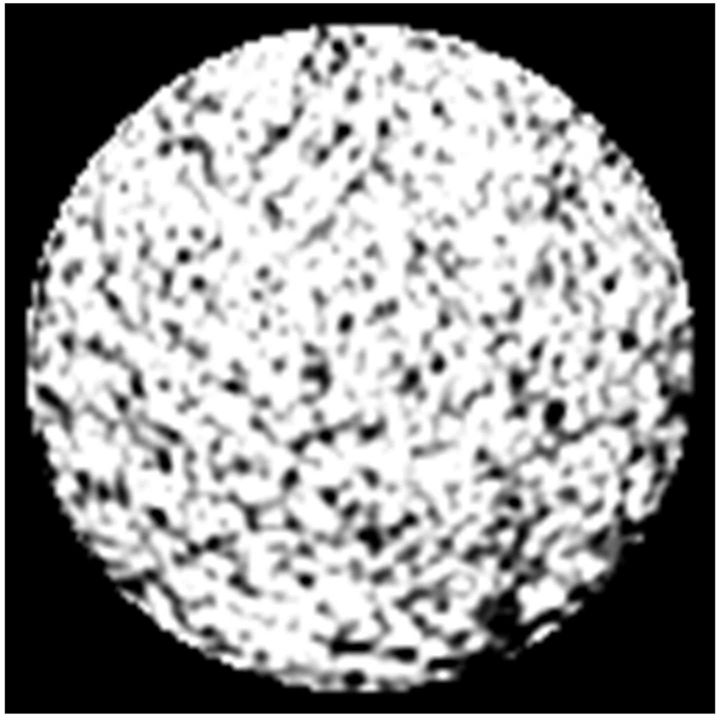
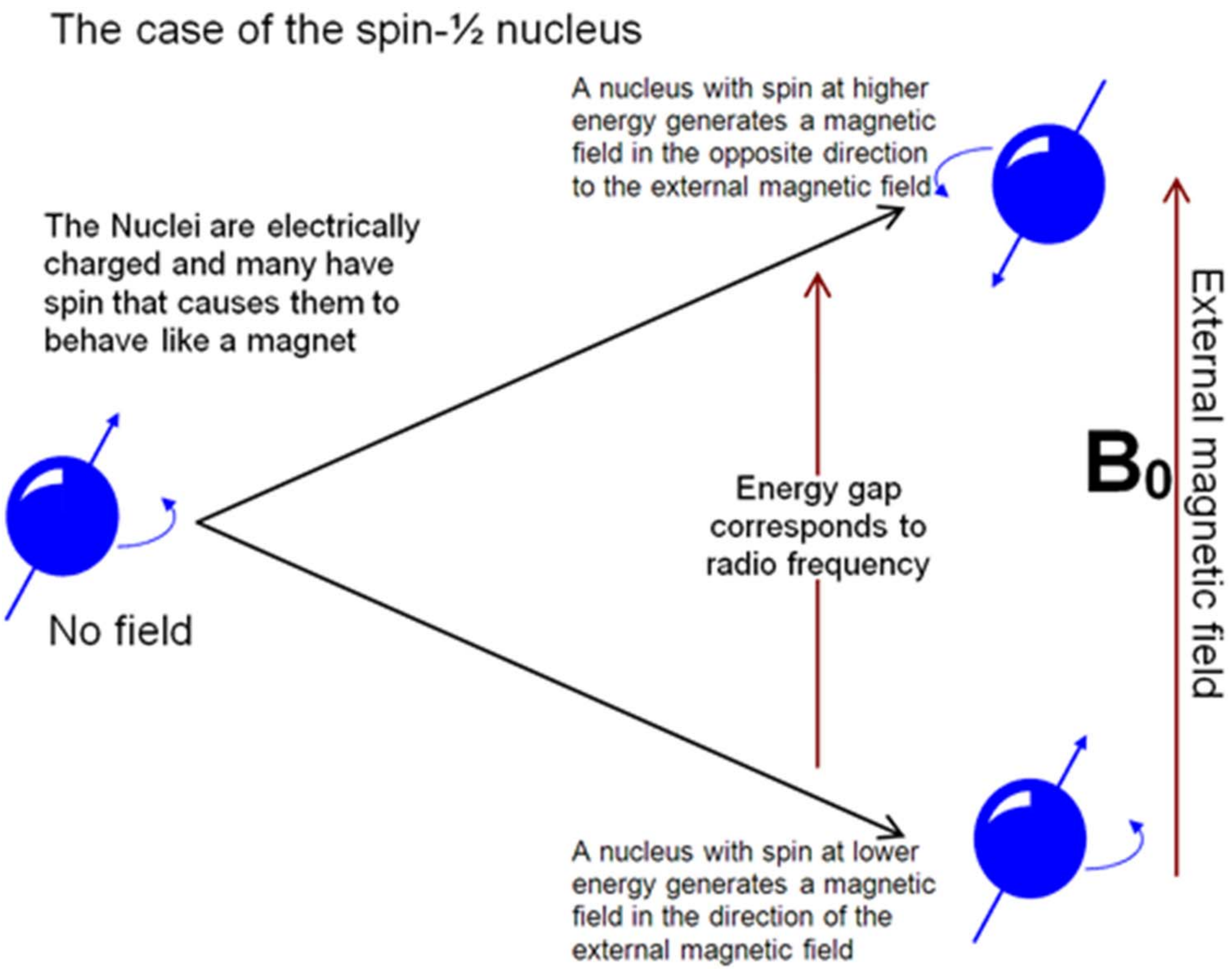
Process Measurements in Microsystems

- Dimensions of the sensor often in the same range than those of the most considerable dimension of the microsystem.
- In this case: fluidic / temperature / reactive (etc) behavior is largely influenced by the sensor or sensor makes it impossible to measure!
- Measuring at the boundary layer / wall is not sufficient
- Non-invasive methods necessary
  - optical (IR, visible, UV-VIS, Raman, X-Ray etc)
  - NMR, MRI



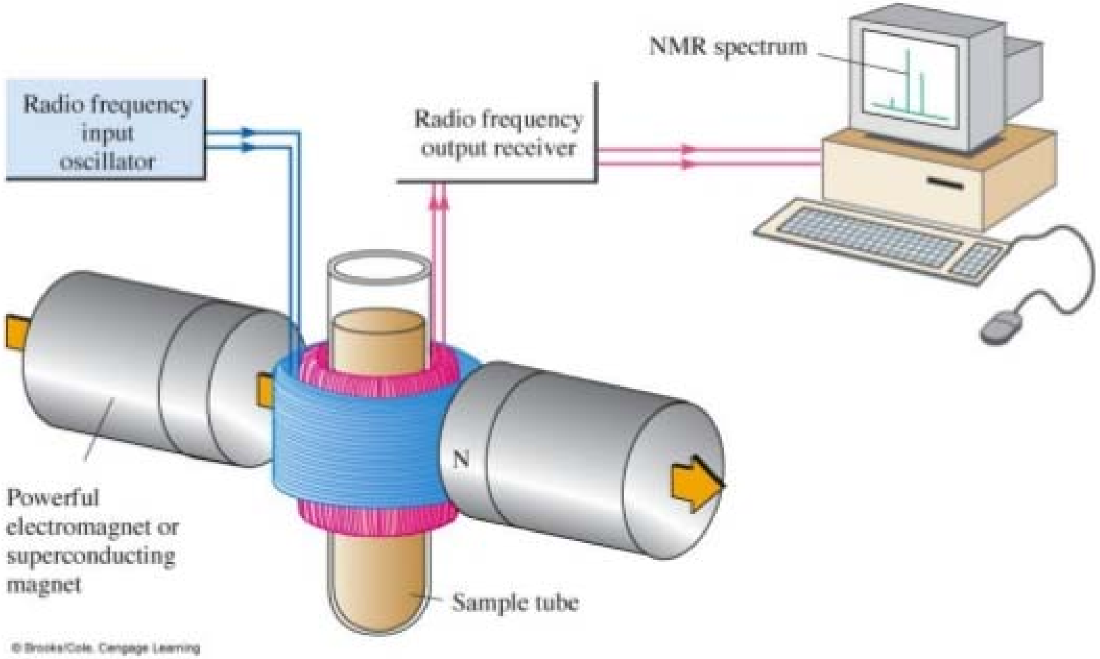
X-ray Tomography of a fluidized catalyst fixed bed reactor.
© HZDR, Dresden, Germany

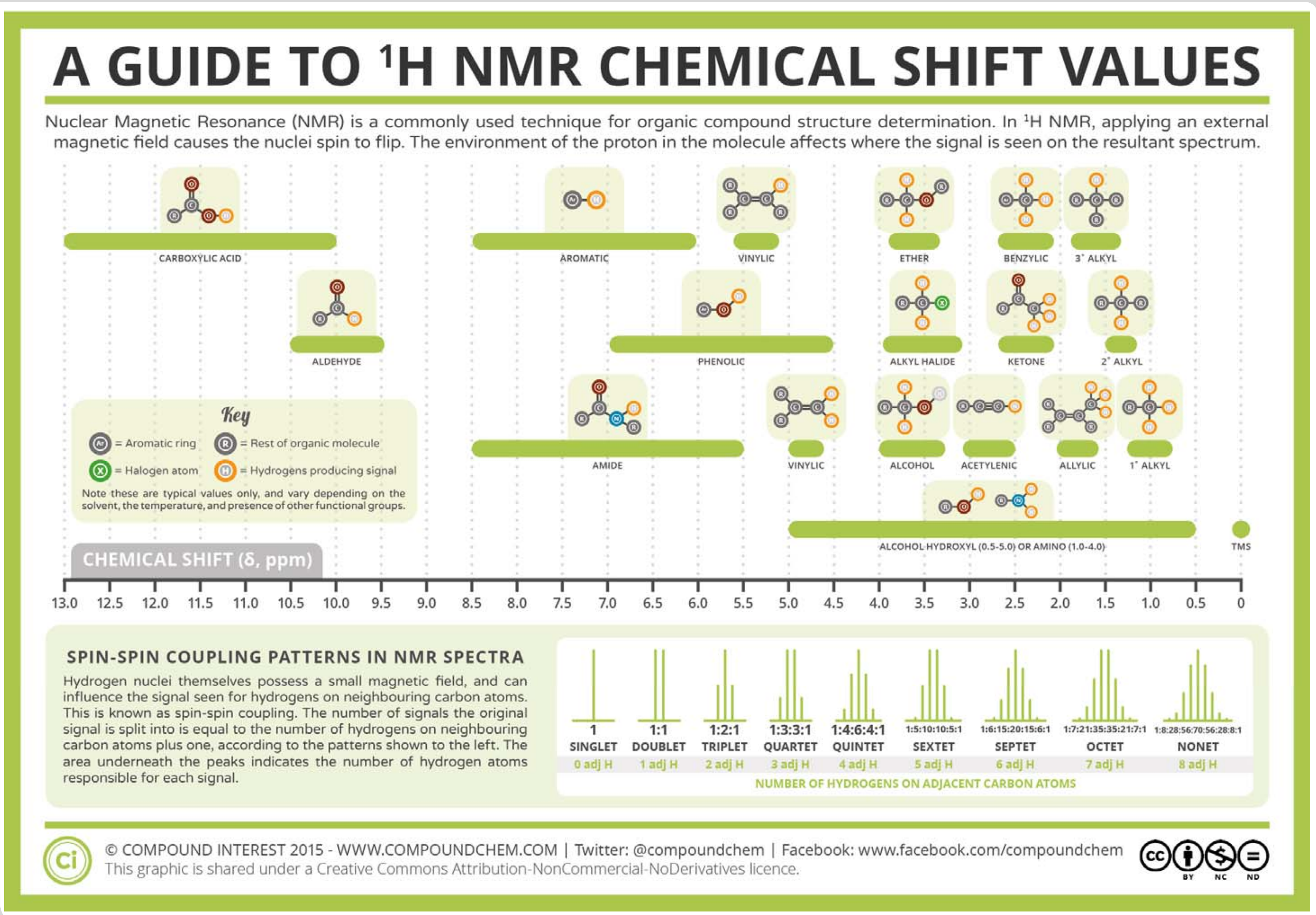
Nuclear Magnetic Resonance NMR



Nuclear Magnetic Resonance NMR

- **Pro's**
  - fast, easy to perform
  - all materials, all states
  - qualitative and quantitative AND structural analysis at the same time
- **Con's**
  - Yet: expensive
  - Not many libraries available yet




A GUIDE TO ¹H NMR CHEMICAL SHIFT VALUES
Nuclear Magnetic Resonance (NMR) is a commonly used technique for organic compound structure determination. In ¹H NMR, applying an external magnetic field causes the nuclei spin to flip. The environment of the proton in the molecule affects where the signal is seen on the resultant spectrum.
CARBOXYLIC ACID
AROMATIC
VINYLIC
ETHER
BENZYLIC
3° ALKYL
ALDEHYDE
PHENOLIC
ALKYL HALIDE
KETONE
2° ALKYL
AMIDE
VINYLIC
ALCOHOL
ACETYLENIC
ALLYLIC
1° ALKYL
ALCOHOL HYDROXYL (0.5-5.0) OR AMINO (1.0-4.0)
TMS
Key
= Aromatic ring
= Rest of organic molecule
= Halogen atom
= Hydrogens producing signal
Note these are typical values only, and vary depending on the solvent, the temperature, and presence of other functional groups.
CHEMICAL SHIFT (δ, ppm)
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
SPIN-SPIN COUPLING PATTERNS IN NMR SPECTRA
Hydrogen nuclei themselves possess a small magnetic field, and can influence the signal seen for hydrogens on neighbouring carbon atoms. This is known as spin-spin coupling. The number of signals the original signal is split into is equal to the number of hydrogens on neighbouring carbon atoms plus one, according to the patterns shown to the left. The area underneath the peaks indicates the number of hydrogen atoms responsible for each signal.
1 SINGLET 0 adj H
1:1 DOUBLET 1 adj H
1:2:1 TRIPLET 2 adj H
1:3:3:1 QUARTET 3 adj H
1:4:6:4:1 QUINTET 4 adj H
1:5:10:10:5:1 SEXTET 5 adj H
1:6:15:20:15:6:1 SEPTET 6 adj H
1:7:21:35:35:21:7:1 OCTET 7 adj H
1:8:28:56:70:56:28:8:1 NONET 8 adj H
NUMBER OF HYDROGENS ON ADJACENT CARBON ATOMS
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Nuclear Magnetic Resonance NMR

Large Scale High Field NMR with 1020 MHz field strength
(= 23.55 T).
National Institute for Material Science,
July 2, 2017
Jeol / NEDO,
Japan

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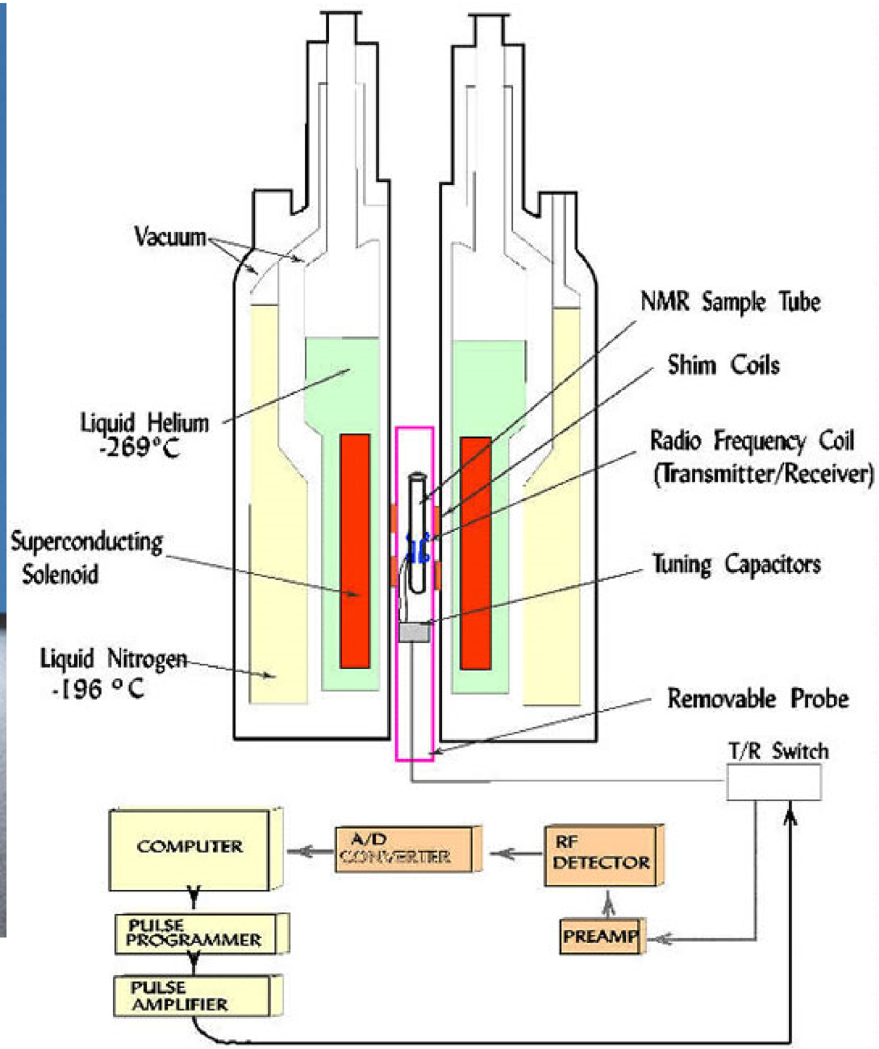
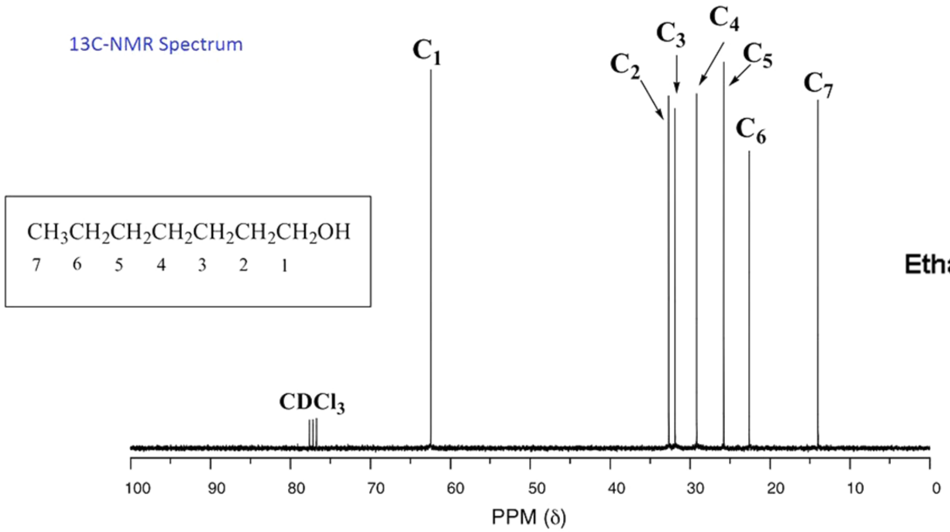
Nuclear Magnetic Resonance NMR

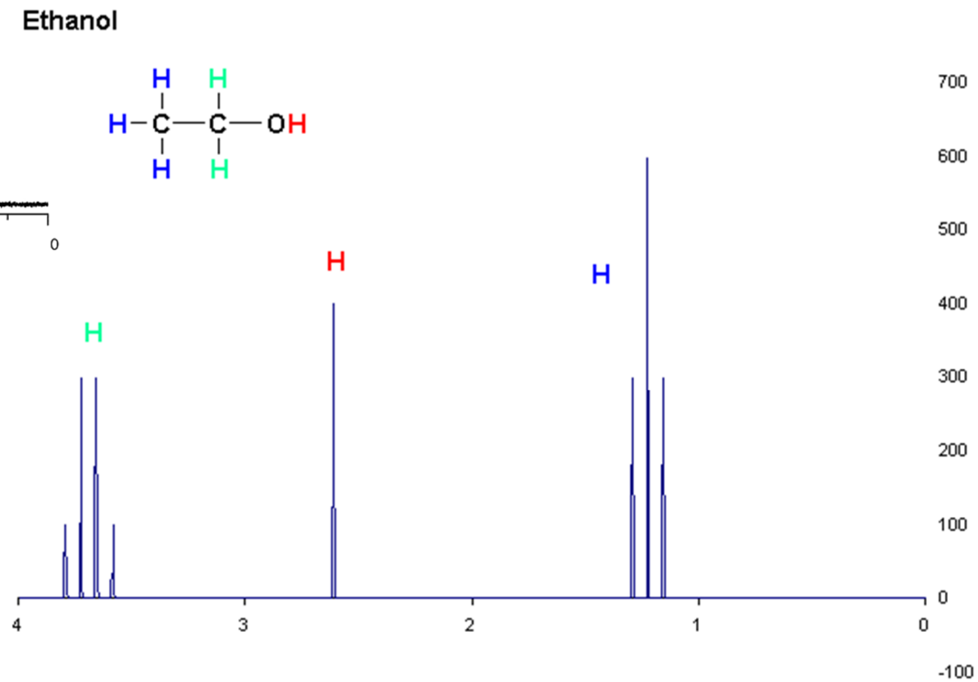


Nuclear Magnetic Resonance NMR

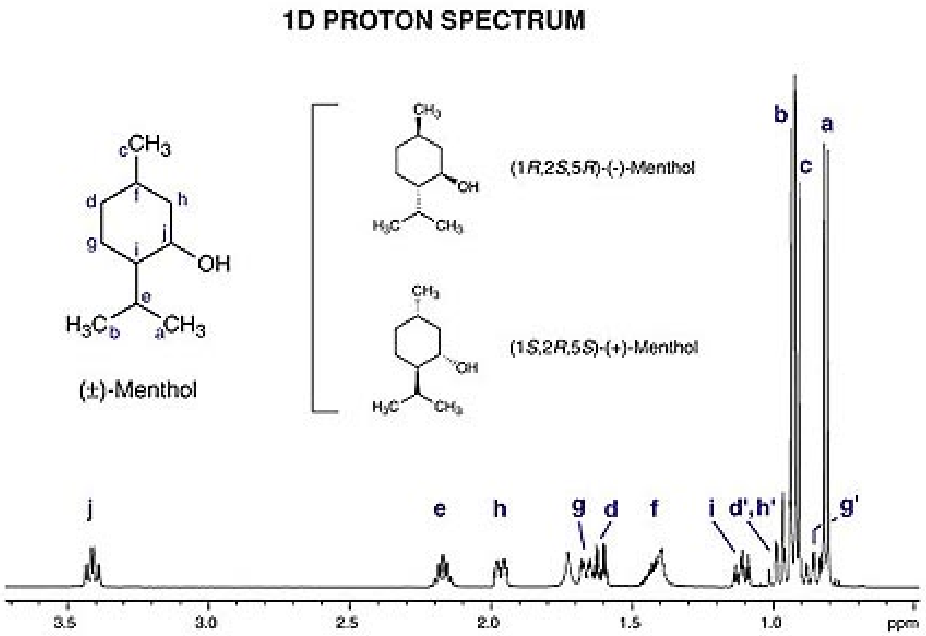
Nuclear Magnetic Resonance NMR

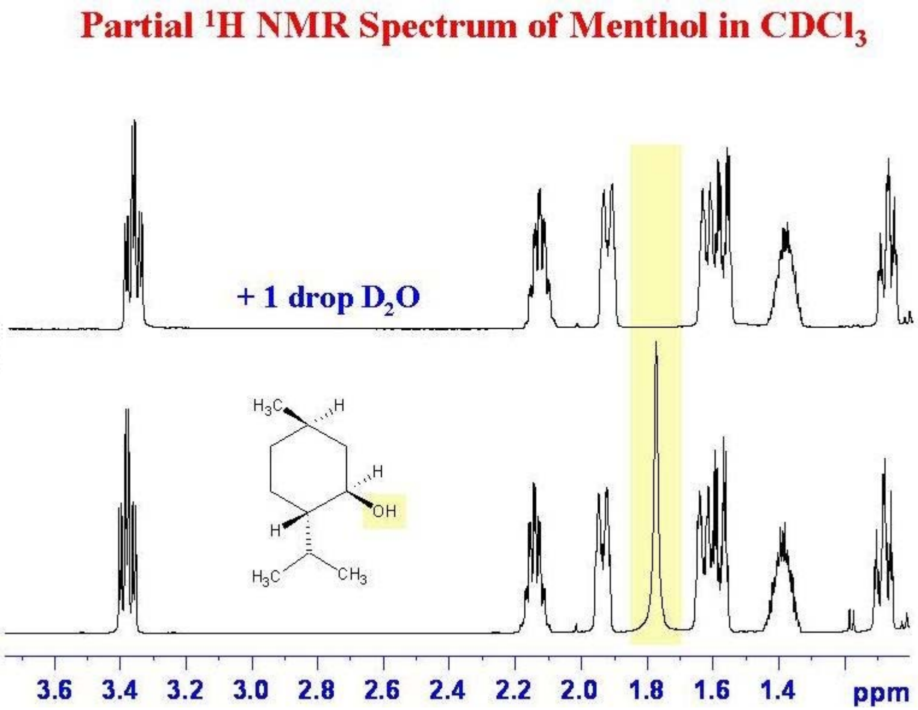
Nuclear Magnetic Resonance NMR



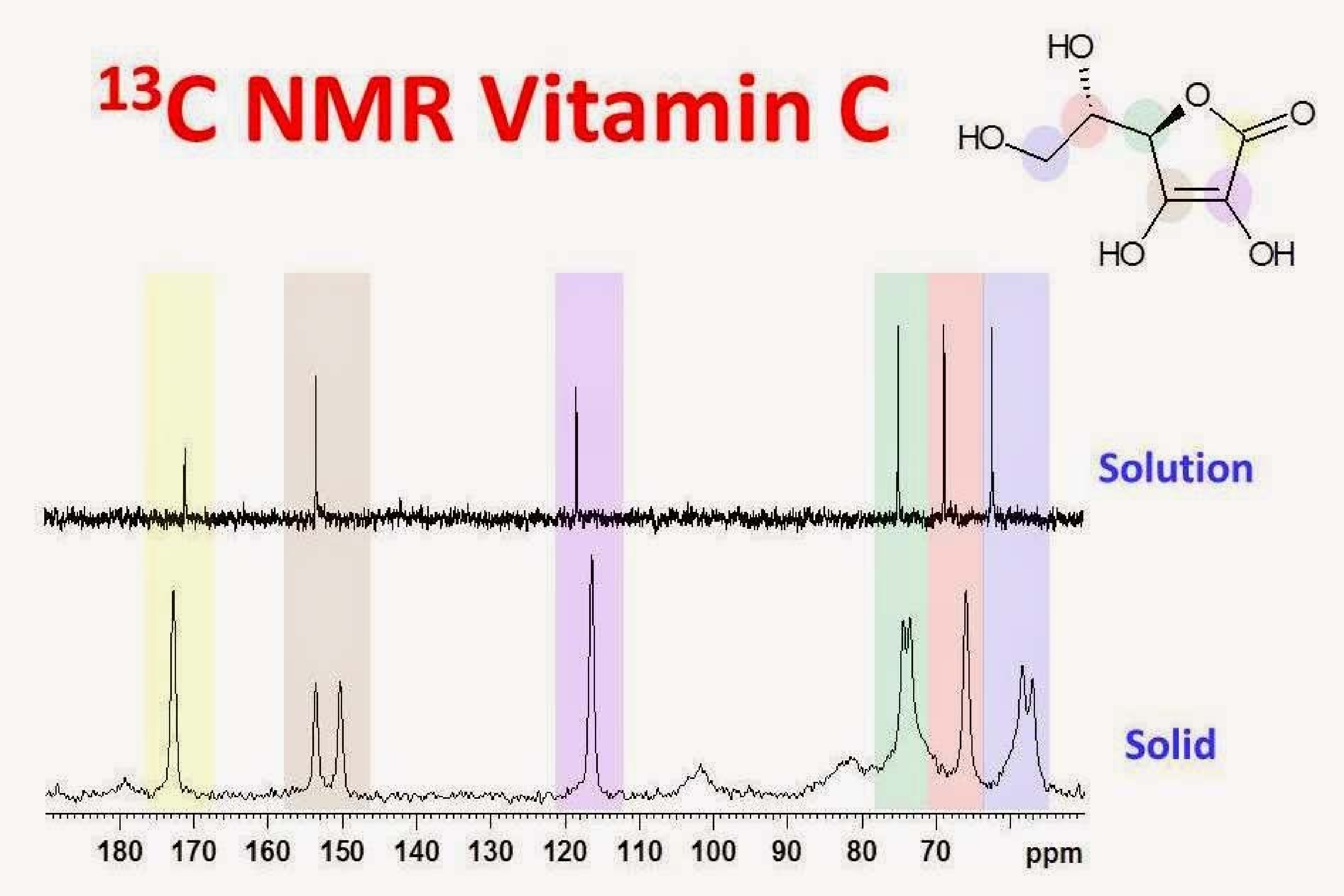


Nuclear Magnetic Resonance NMR

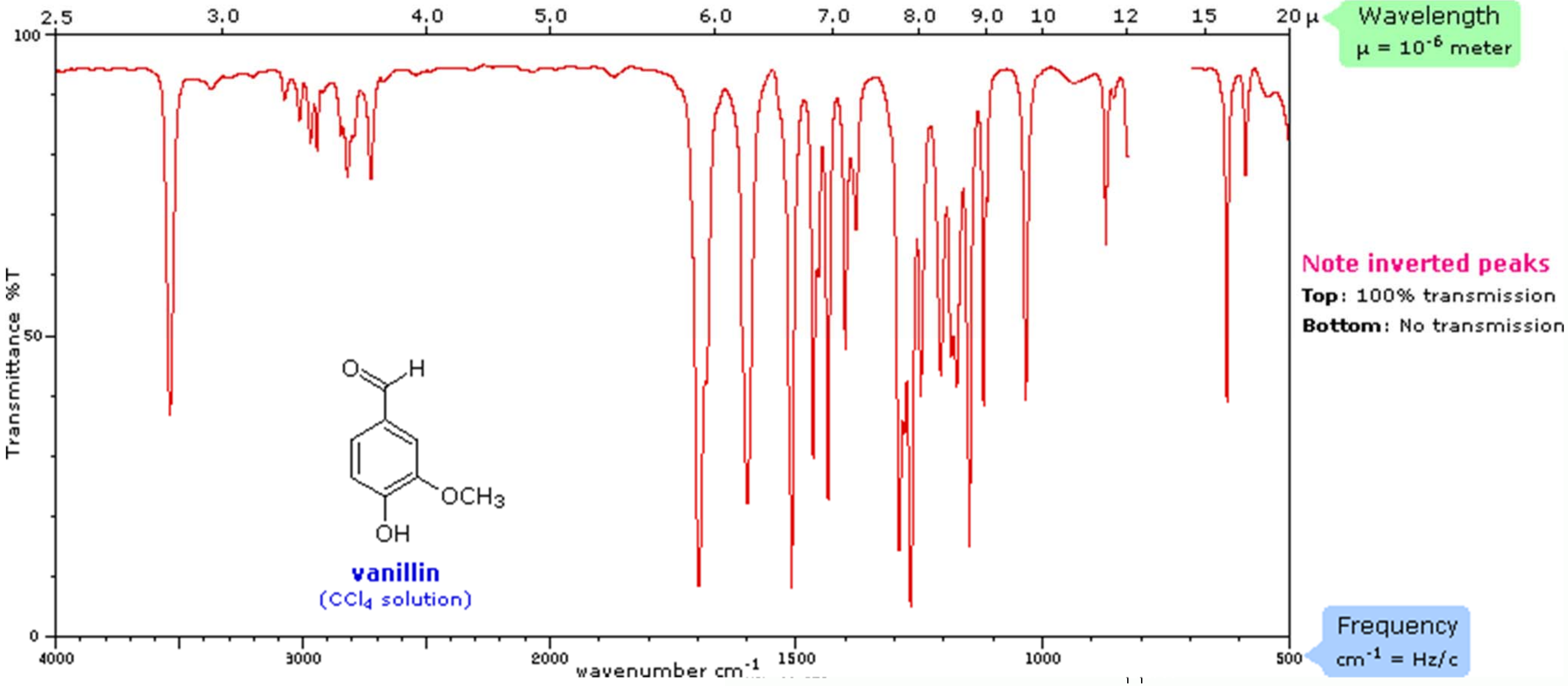


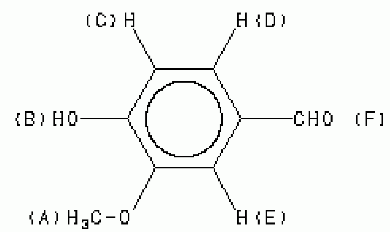


Nuclear Magnetic Resonance NMR



Nuclear Magnetic Resonance NMR

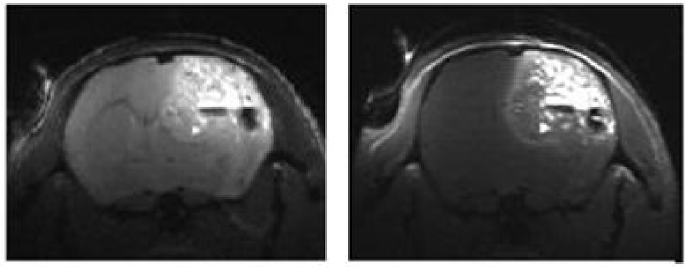




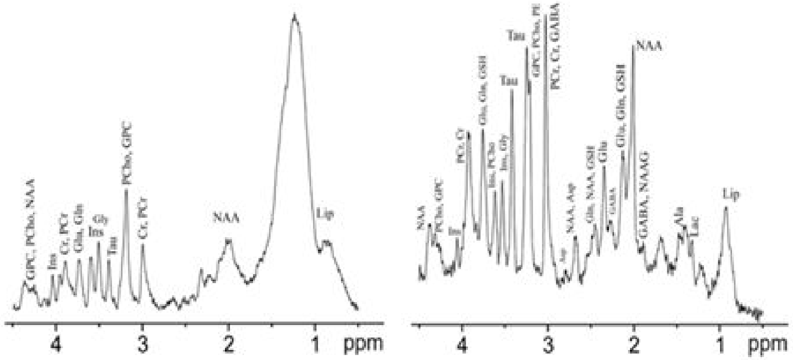
Location	Shift (ppm)
A	3.959
B	6.39
C	7.047
D	7.42
E	7.42
F	9.823

Nuclear Magnetic Resonance NMR

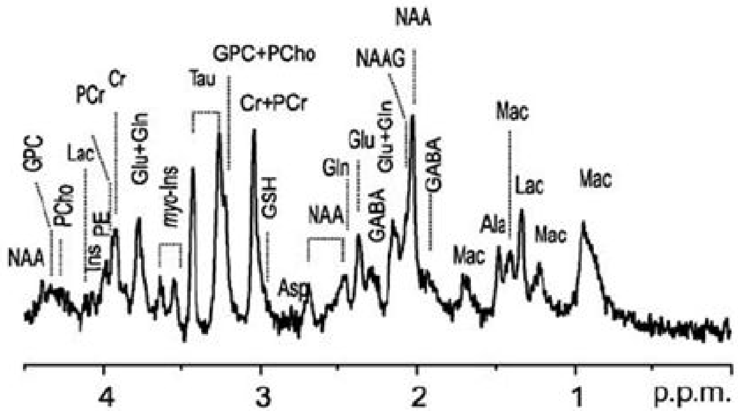
Mouse brain

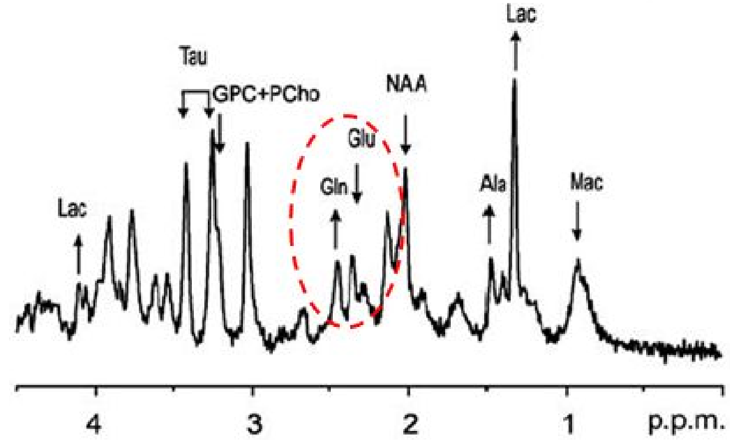


Mouse model of human glioma

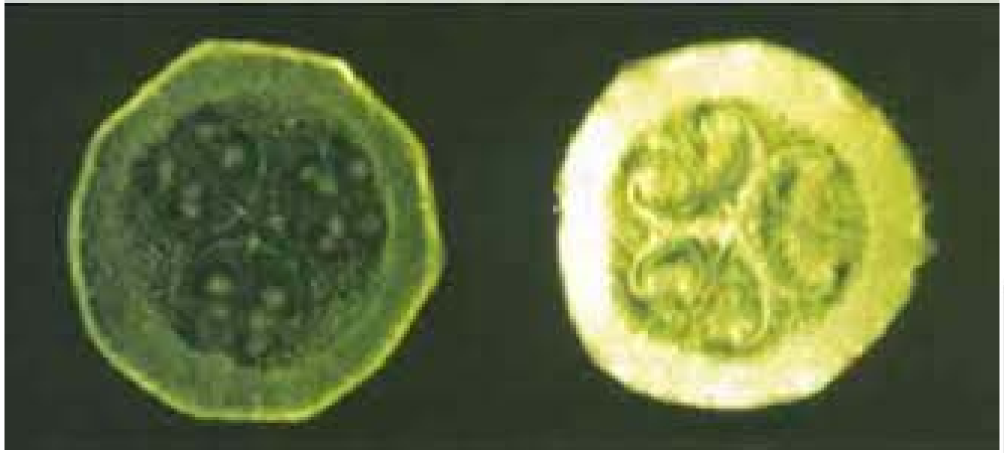


Mouse model of stroke

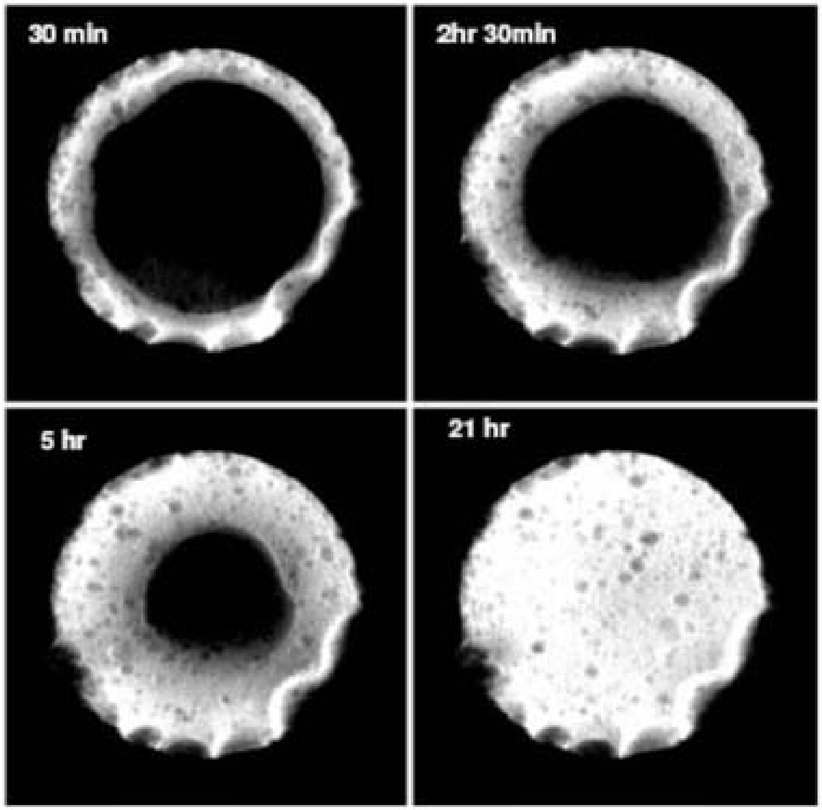




Nuclear Magnetic Resonance NMR



MRI of a cut fruit: left shows the fresh fruit, right a frozen fruit



Continuous MRI of drug delivery using polyethylen glycol derivates with mid-term time resolution

Process Measurements in Microsystems

- Thermal Process Engineering

Parameter	Unit	Range
Temperature T Temperature Difference ΔT	K	0.1…2000 (absolute T) some 0.1…some 100 (difference)
Pressure P Pressure Difference ΔP	Pa	1…100 x 10^6 (absolut P) some…some 10^7 (difference)
Mass flow $\dot{m}$ Volume flow $\dot{V}$ Mean flow velocity $\overline{w}$	g s^{-1} m^3 s^{-1} m s^{-1}	some 10^{-9} … some 10^9 some 10^{-15} … some 10^2 some 10^{-4} … some 10^2
Density ρ	kg m^{-3}	some 10^{-12} (high vacuum)… some 10^4 (solids)
Viscosity; dynamic η kinematic ν	kg m^{-1} s^{-1} m^2 s^{-1}	some 10^{-5} (hydrocarbons)… some 10^{18} (crystals)
Geometric dimensions, Phase and Phase changes, Chemical reactivity (pH), Particle content, Abrasivity, Sedimentation & Fouling tendency, etc.		
In OPTIMUM case: time and spatial profiles (distribution) of all the named values!		

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Process Measurements in Microsystems

- ***Chemical*** Process Engineering

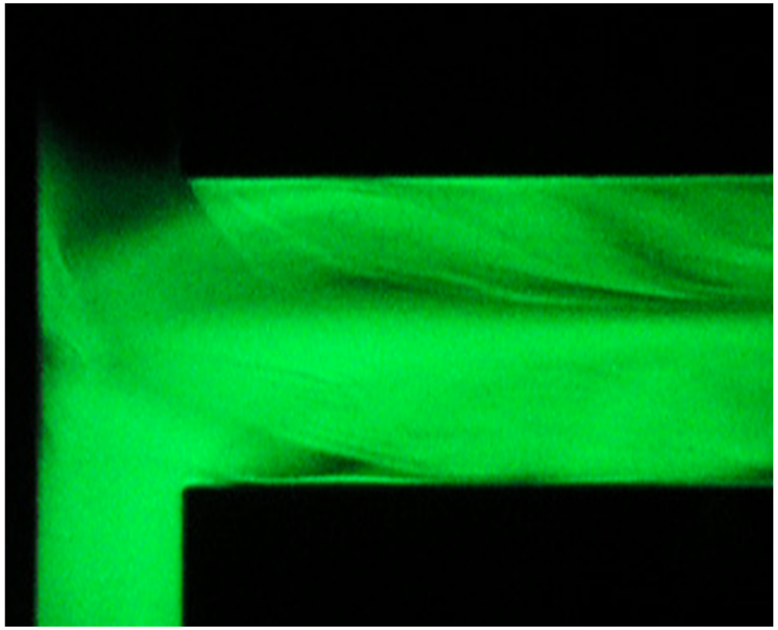
ALL parameters named for Thermal Process Engineering, and additionally:

Parameter	Unit	Range
(electro-) Chemical Potential μ	$G = \frac{J}{mol}; J$	$-10^4 \ldots 10^4$ G; G: Gibbs = J/mol
Selectivity of reaction S	-	0…1
Reactand concentration; Product concentration	$g\ l^{-1}$; $mol\ l^{-1}$	some 10^{-9} … some 10^3; some 10^{-9} … some 10^4
Thermal input / output	$J\ mol^{-1}$; $J\ g^{-1}$	some -10^6 (exotherm)… some $+10^6$ (endotherm)
Volume changes & Pressure changes, Phase and Phase changes, Precipitation, Color changes, Optical spectra, light emissions (luminescence, fluorescence), pH, etc		
In OPTIMUM case: time and spatial profiles (distribution) of all the named values!		

Process Measurements in Microsystems

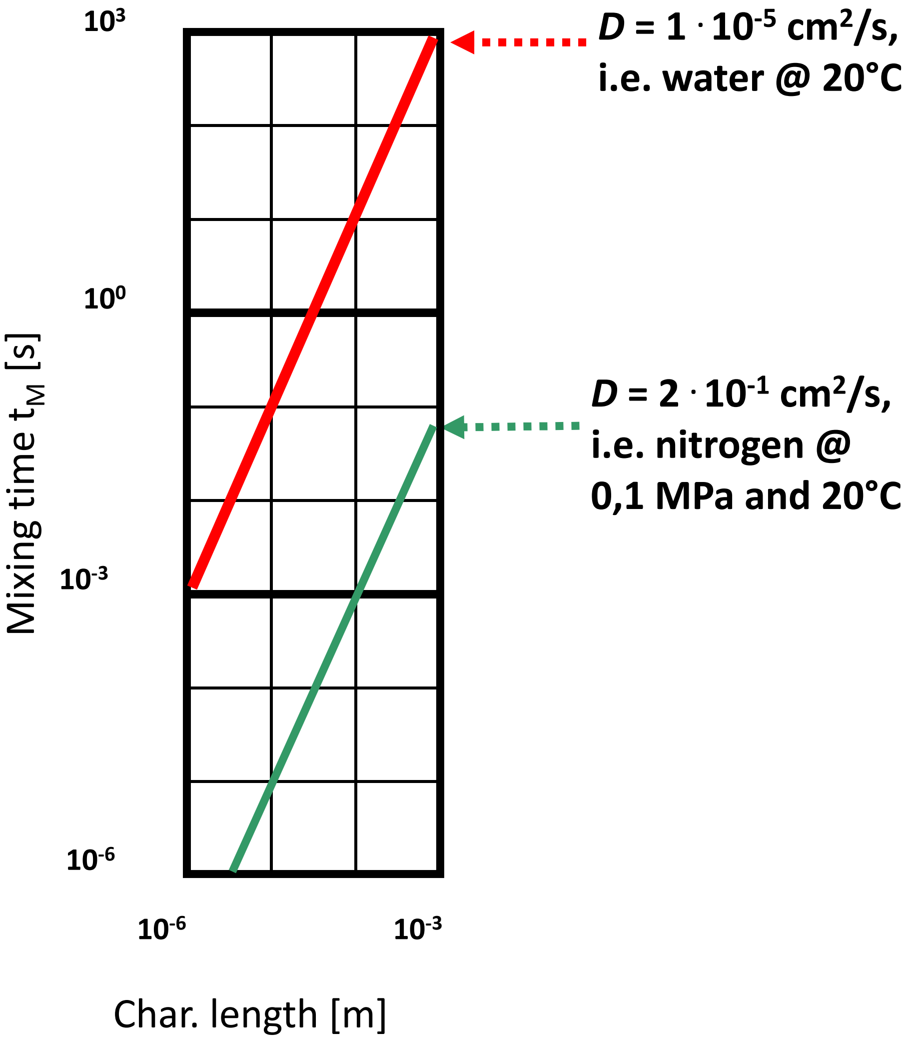
- Limitation #1: *Time resolution high enough?*
  - Example: A mixing process shall be followed, total mixing shall be achieved and characterized.
  - Diffusive mixing in a T-micromixer, dimensions of the T-piece are sub-millimeter.
  - Diffusion time: $\tau_m = \frac{x^2}{2 \cdot D}$

    with t_m mixing time [s]
    x characteristic dimension [m]
    D diffusion coefficient $\left[\frac{m^2}{s}\right]$
  - **Liquids: t_m ≈ some ms (for x some ten µm)**
  - **Gases: t_m ≈ some µs (for x some ten µm)**



Schlüter et al., TUHH, 2014

Process Measurements in Microsystems



Mass transfer by diffusion:

$$t_M = \frac{x^2}{2 \cdot D}$$

t_M	Mixing time	$[s]$
x	Char. length	$[m]$
D	Diffusion coeffi.	$\left[\frac{m^2}{s}\right]$

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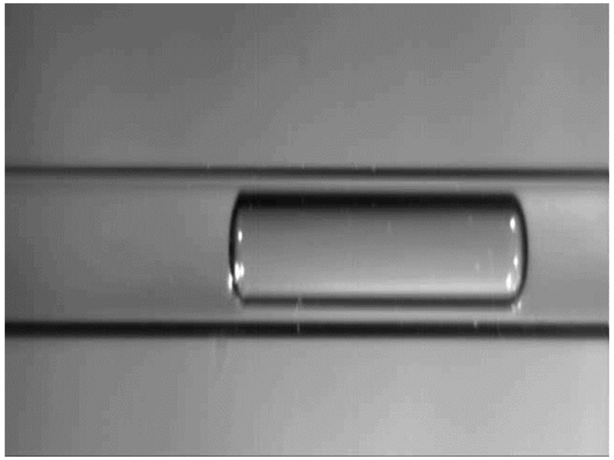
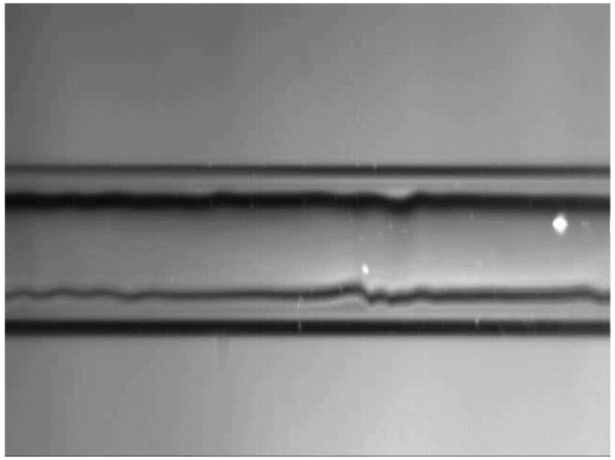
Process Measurements in Microsystems

- Limitation #2: *Spatial resolution high enough?*
  - Example: Flow and chemical characterization inside a microchannel (SlowMotion: 100x).



100 µm Plug Flow



100 µm Slug Flow

100 µm Annular Flow

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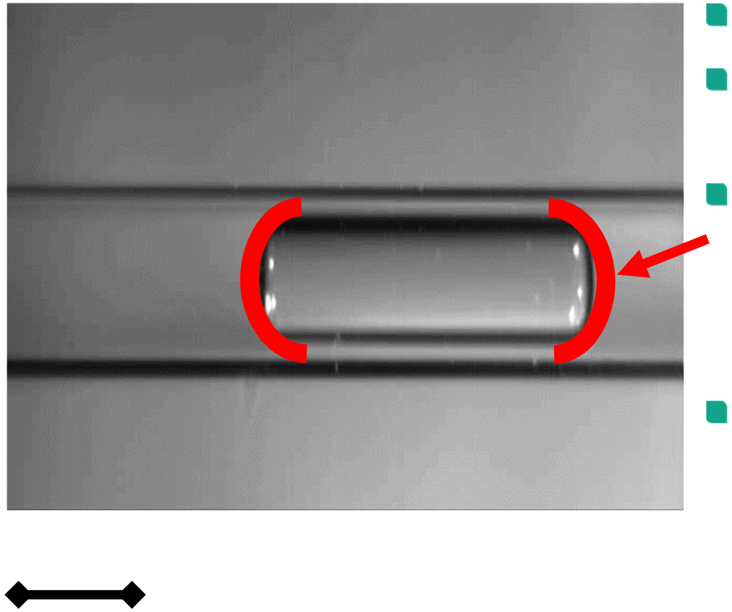


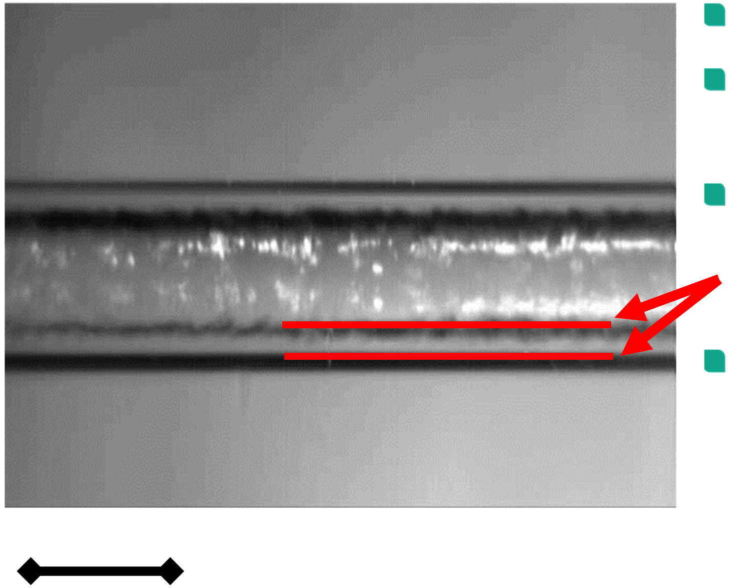
100 µm Plug Flow

Haas-Santo et al., KIT-IMVT, 2015

- Spatial Resolution high enough to characterize flow!
- Areas of interest for chemical reaction: Concentration gradients are maximized!
- Thickness of layer to be chemically characterized: some 10nm…some µm (depending on tube diameter, surface tension & contact angles, flow speed, density ratio etc.)
- Measurement close to tube walls: not well-defined due to surface effects of wall material.

Process Measurements in Microsystems

- Limitation #2: *Spatial resolution high enough?*
  - Example: Flow and chemical characterization inside a microchannel (SlowMotion: 100x).



100 µm Annular Flow

Haas-Santo et al., KIT-IMVT, 2015

- Spatial Resolution high enough to characterize flow!
- Areas of interest for chemical reaction: Concentration gradients are maximized!
- Thickness of layer to be chemically characterized: some 10nm…some µm (depending on flow speed, density ratio)
- Measurement close to tube walls: not well-defined due to surface effects of wall material.

Process Measurements in Microsystems

- Limit #1: *Time Resolution of NMR/MRI high enough?*
  - Medical Applications / in-vivo NMR/MRI: 100 ms reached easily (see: Lin et al., doi: 10.1016/j.neuroimage.2012.01.072), but spatial resolution is slightly reduced then
  - New developments in BioMed: 20 ms MRI time resolution possible (see: Uecker et al., doi: 10.1002/nbm.1585)
  - In Solids: 3 µs possible! (see: Powles & Strange, Proc. Phys. Soc., 82, 1, 1963(!!!))
  - 50 ps time resolution reached!!! (see Xi et al., doi: 10.1109/LMAG.2016.2536661)
  - For Process Engineering objectives:

    ???

    What about hyper-polarization?
  - Pre-Consideration: SNR!

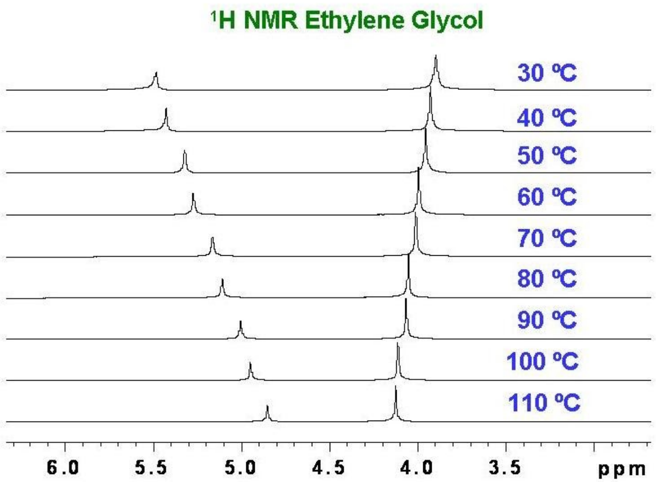
Process Measurements in Microsystems

- Limitation #2: *Spatial Resolution of NMR/MRI high enough?*
  - Medical Applications / in-vivo NMR/MRI: Down to 10µm reached (see: Köckenberger et al., https://doi.org/10.1111/j.0022-2720.2004.01351.x)
  - Also, Bruker names spatial resolution of about 10µm for commercially available NMR systems (see: https://www.bruker.com/fileadmin/user_upload/8-PDF-Docs/MagneticResonance/MRI/brochures/MRI_Application_Solutions.pdf)
  - ***90nm*** spatial resolution achieved (see: https://www.google.de/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact=8&ved=0ahUKEwj15vqCyeHaAhWJBSwKHWk4AjEQFggsMAA&url=https%3A%2F%2Farxiv.org%2Fpdf%2Fcond-mat%2F0702664&usg=AOvVaw1W0ehZ8gdZ3J4seF94taHO)
  - For Process Engineering objectives:
    Probably the spatial resolution is high enough in many cases!
  - Pre-Consideration: SNR!

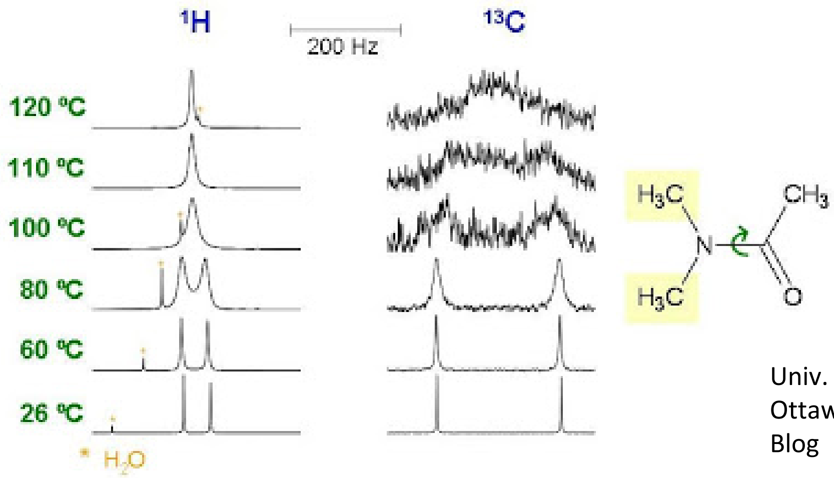
Process Measurements in Microsystems

- Process Engineering Parameters: T

Parameter	Measurable with NMR?	Comments
Temperature T Temperature Difference ΔT	Yes	Contactless measured by temperature-dependent resonance shift, see i.e. Amann et al., J. Magn. Res. 46, 1982; Parker et al., Med. Physics 10(3), 1983; NMR-Thermometer: http://chem.ch.huji.ac.il/nmr/software/thermometer.html



Univ. of Ottawa NMR Blog



Univ. of Ottawa NMR Blog

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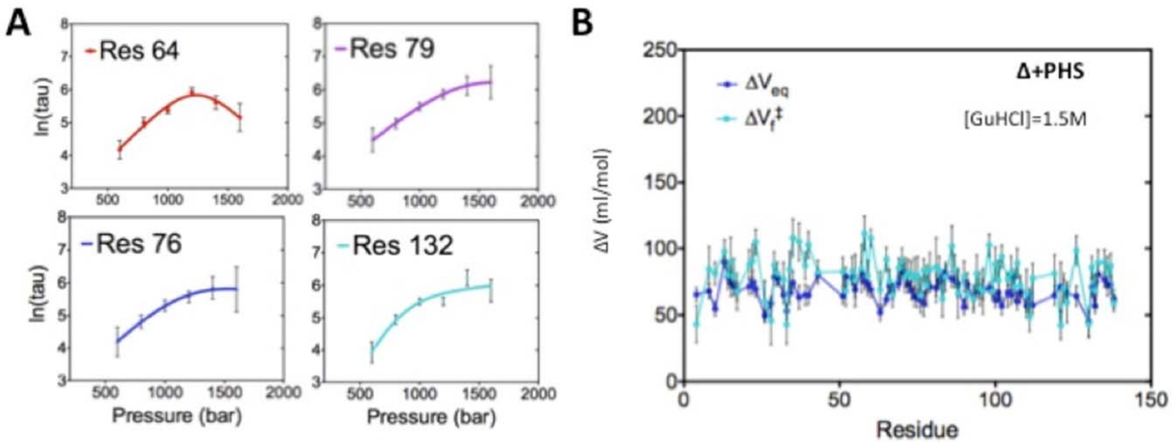
Process Measurements in Microsystems

- Process Engineering Parameters: P

Parameter	Measurable with NMR?	Comments
Pressure P Pressure Difference ΔP	Not directly!	Materials with pressure-dependent relaxation time changes; see i.e. Kleinberg, Magn. Res. Imag. 14(7-8), 1996

However: The advantage of the non-invasive NMR measurement is NOT given, in most cases: combination of NMR measurements (for other objectives) and conventional capillary pressure measurements; see i.e. http://petrowiki.org/NMR_petrophysics

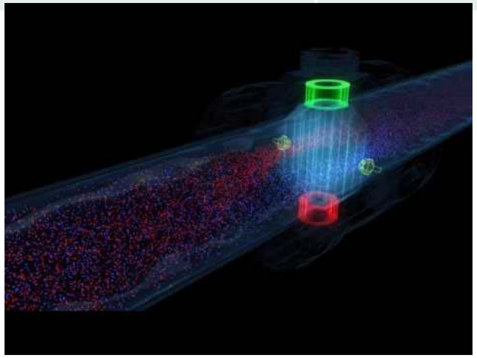


www.cbs.cnrs.fr

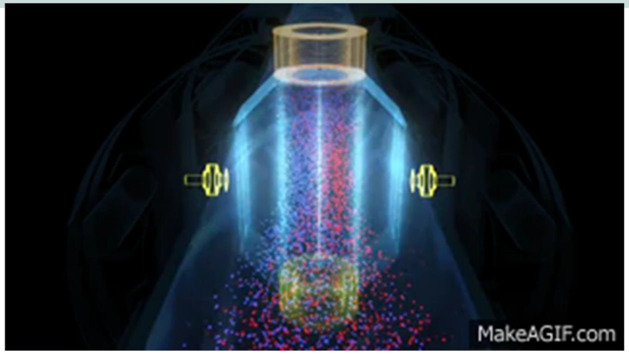
Process Measurements in Microsystems

- Process Engineering Parameters: Several others

Parameter	Measurable with NMR?	Comments
Mass flow $\dot{m}$ Volume flow $\dot{V}$ Mean flow velocity $\overline{w}$	Yes	Can be measured contactless & simultaneous; see i.e. Krüger et al., Flow Meas. Instr. 7(1), 1996; Thorn et al., Meas. Sci. Tech. 8(7), 1997; More recent: https://www.youtube.com/watch?v=EuOoyqYbKQI https://www.youtube.com/watch?v=GY8Er6dJEZc
Density ρ	Yes	
Viscosity; dynamic η kinematic ν	Yes	
Phase and Phase changes, Particle content	Yes	



Endress & Hauser



Process Measurements in Microsystems

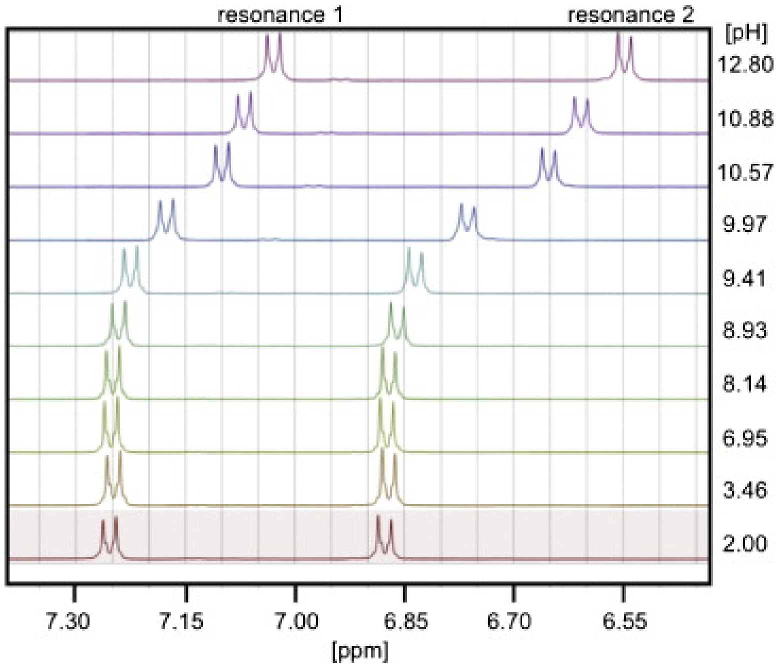
- Process Engineering Parameters: Several others more

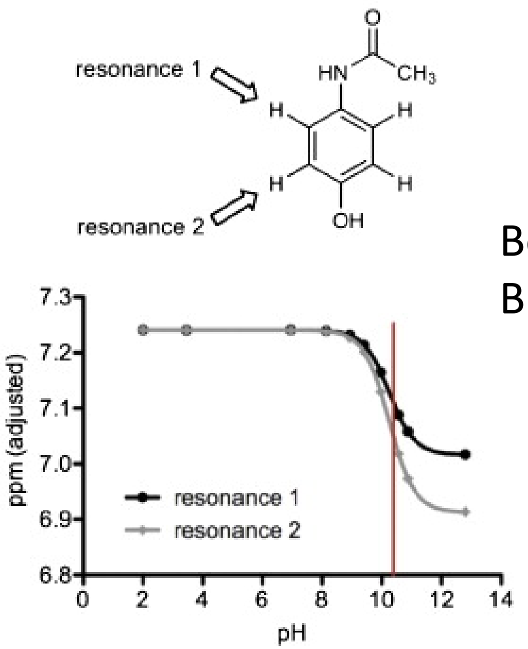
Parameter	Measurable with NMR?	Comments
(electro-) Chemical Potential μ	Yes	Relaxation time changes with the chemical potential, see i.e. Weber & Kimmich, Macromolecules, 26(10), 1993; https://qa.nmrwiki.org/question/173/chemical-potential-by-nmr
Selectivity of reaction S	Not directly	As in conventional measurements, only via ratio of (by-)products!
Reactand concentration; Product concentration	Yes	Well known…
Thermal input / output	Not directly	As in conventional measurements, only via temperature decrease / increase

Process Measurements in Microsystems

- Other Process Engineering Parameters

Parameter	Measurable with NMR?	Comments
pH, pK_a	Yes	Measuring the active protons, See i.e. Bezençon et al., J. Pharm. BioMed. Anal. 93, 2014





Bezençon et al., J. Pharm. BioMed. Anal. 93, 2014

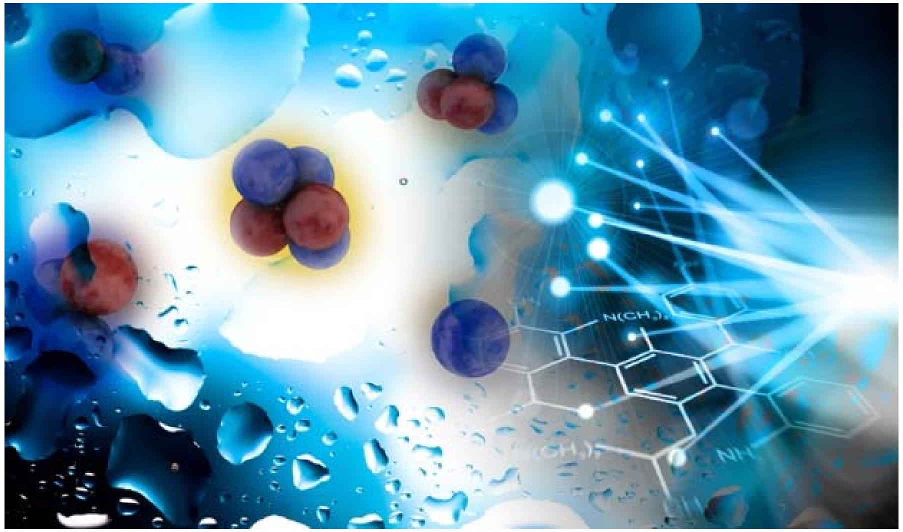
Process Measurements in Microsystems

- Measuring the Chemical Potential is extremely interesting!

$$dG = -SdT + VdP + \sum_{i=1}^{n} \mu_i dN_i$$

  - G: Gibbs-Energy, S: Entropy, V: Volume, μ_i: Chemical Potential of component „i“, N_i: Number of molecules of component „i“.

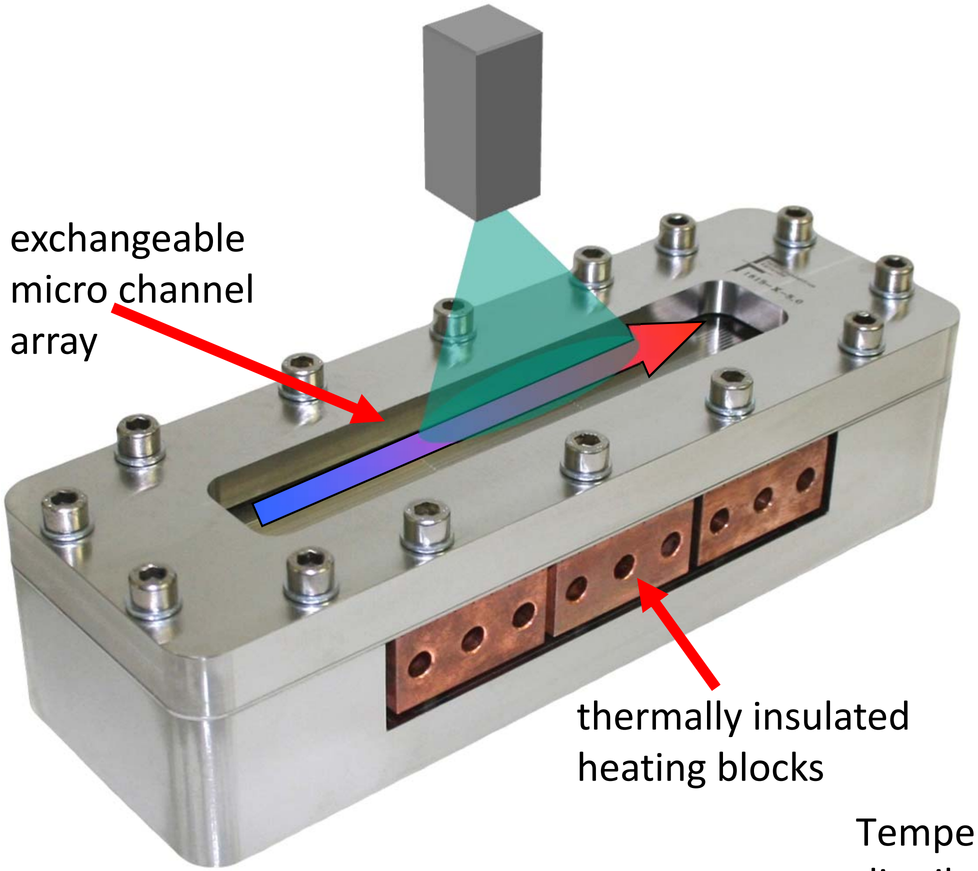
- Keeping several parameters constant allows to directly distinct the others in a row of measurements.
  This may lead to a ***full*** thermodynamical description of a process.



Visualization

KIT / IMVT

- Conventional: High efforts necessary



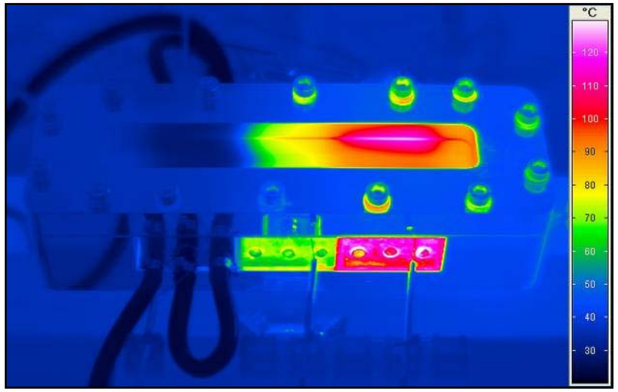
Observation:

- Microscope
- High-speed camera
- f_{max} ~ 200 000 fps

Process settings:

- Microchannels
- Mass flow, pressure
- Heat flux / temperature
- Fluid

Temperature distribution

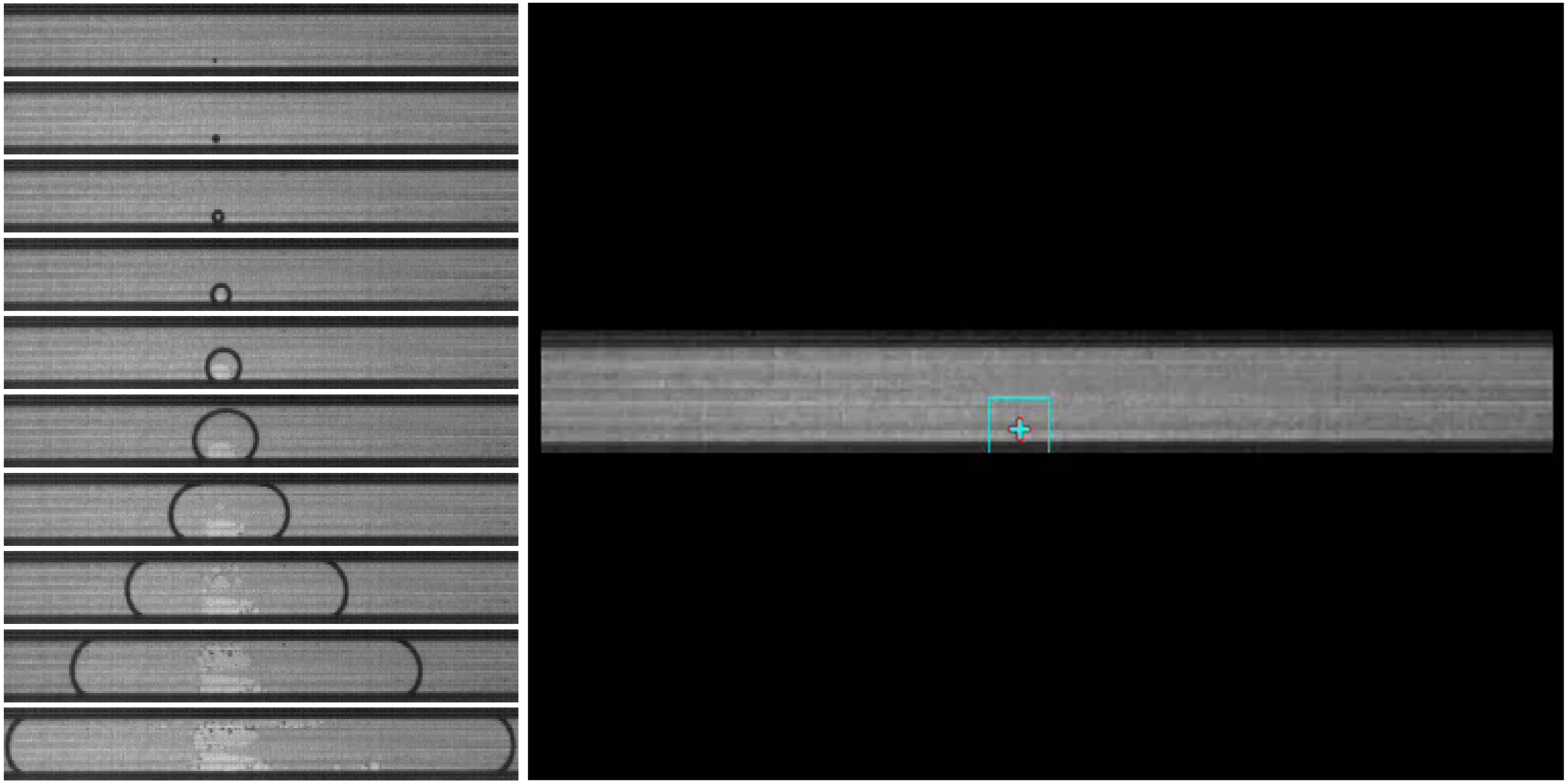


Visualization

KIT / IMVT

- Phase transition: Following a single bubble in a micro channel

$\Delta_{picture} = 3.8 \cdot 10^{-3}$ s



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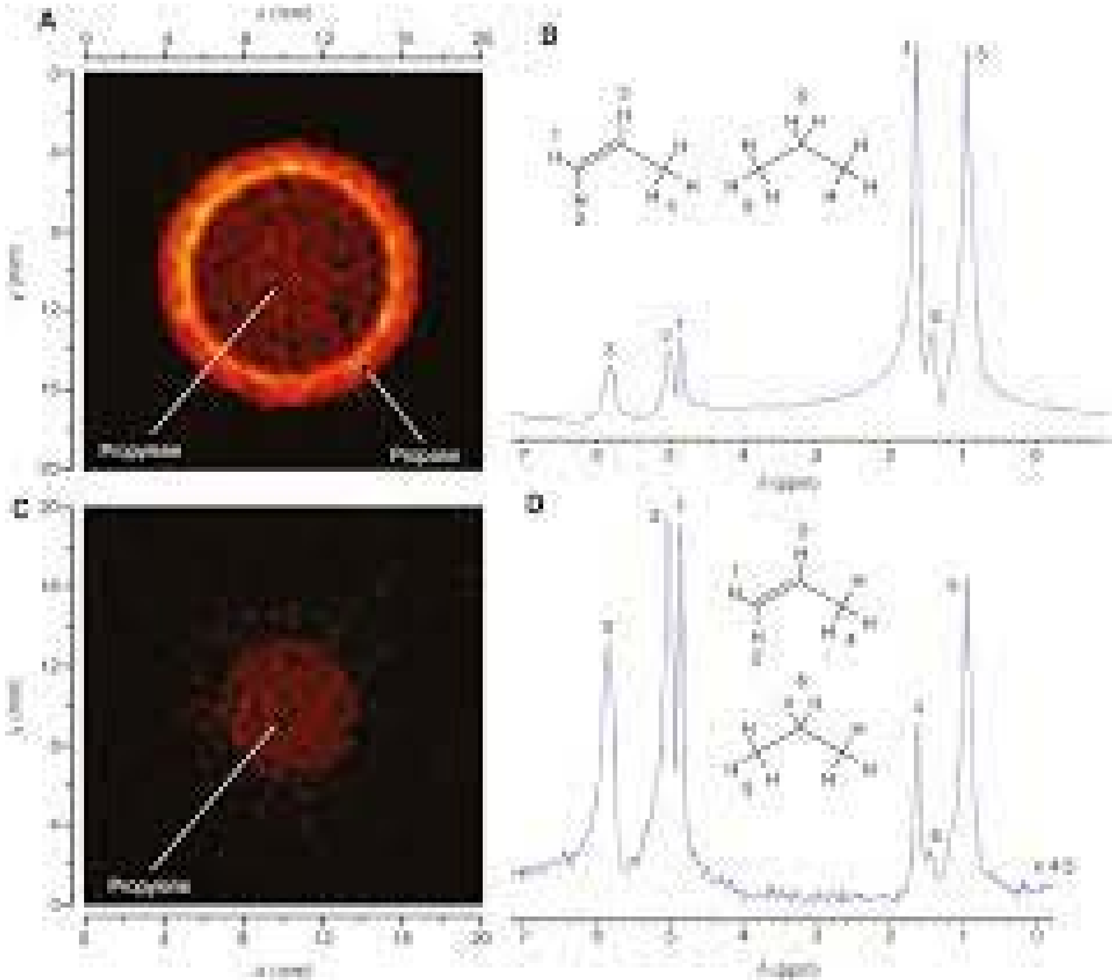
NMR Visualization

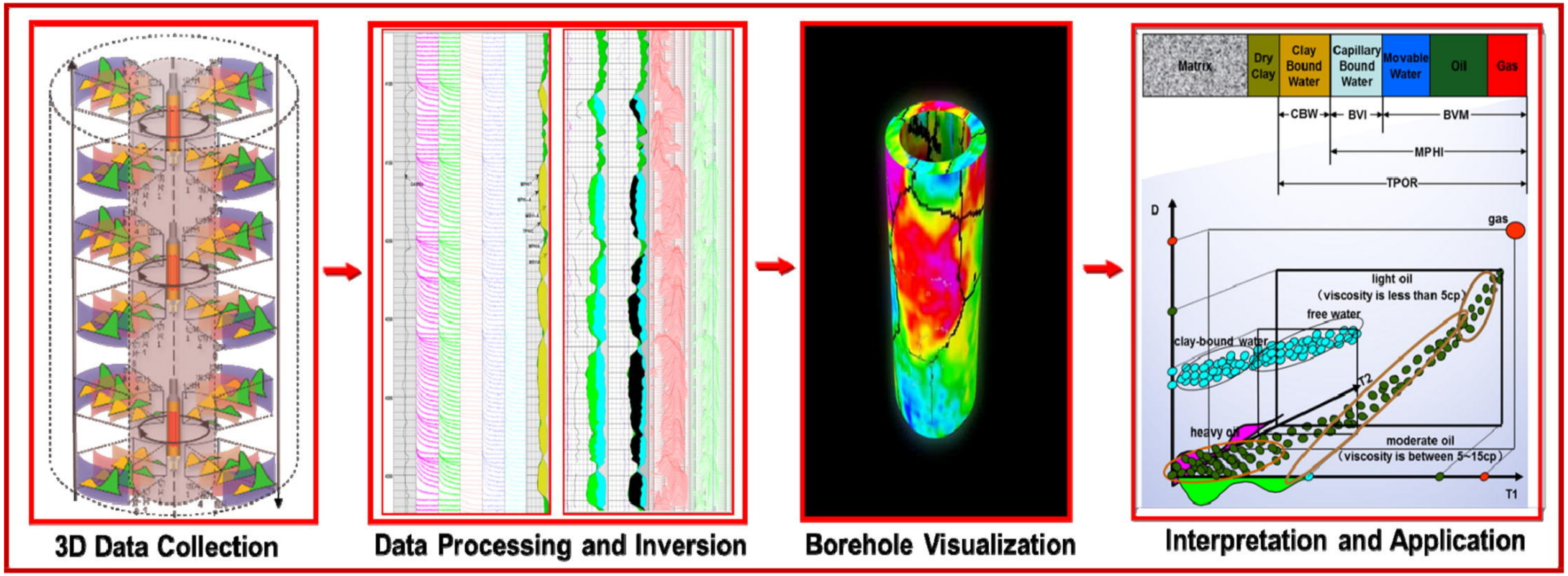
- Flow visualization of catalytic processes



http://doi.org/10.1515/revce-2018-0035

NMR Visualization

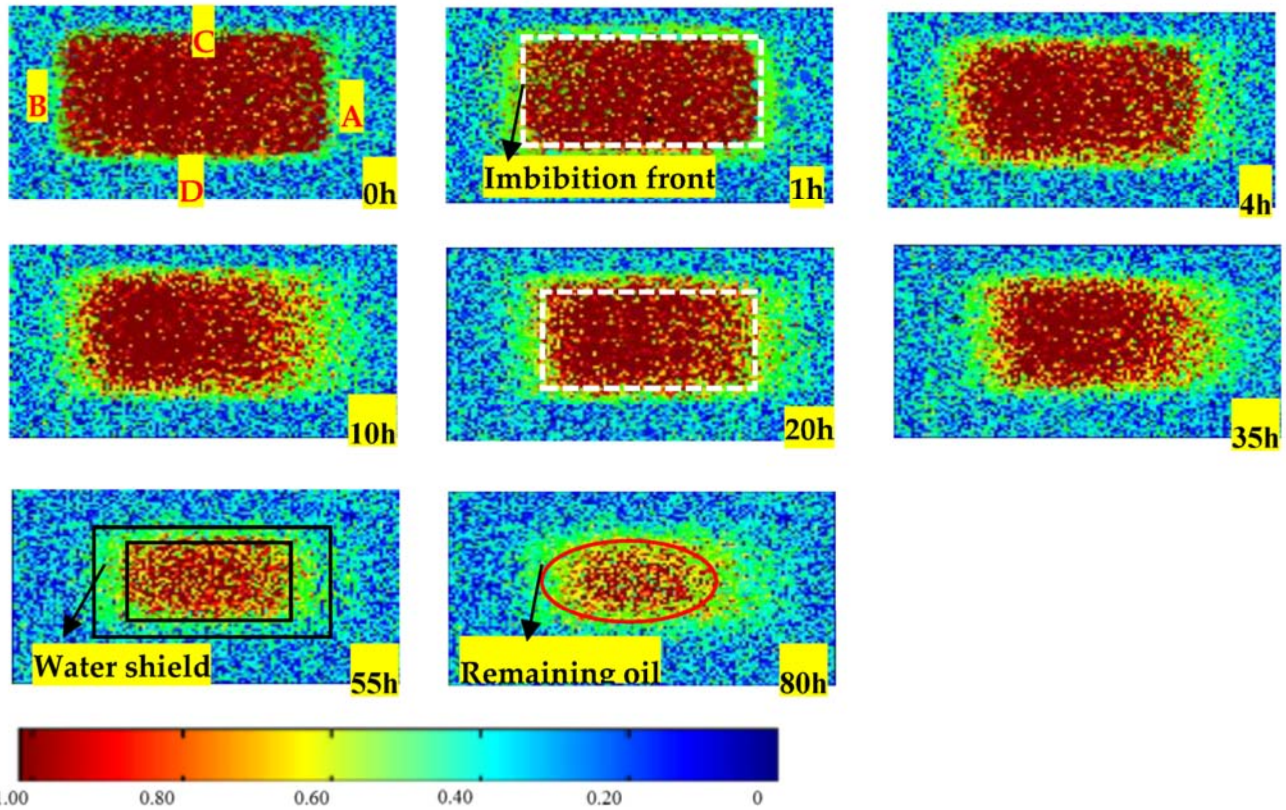
- Flow visualization: Geophysics



Borehole Nuclear Magnetic Resonance Study at the China University of Petroleum https://doi.org/10.1016/j.jmr.2021.106914

NMR Visualization

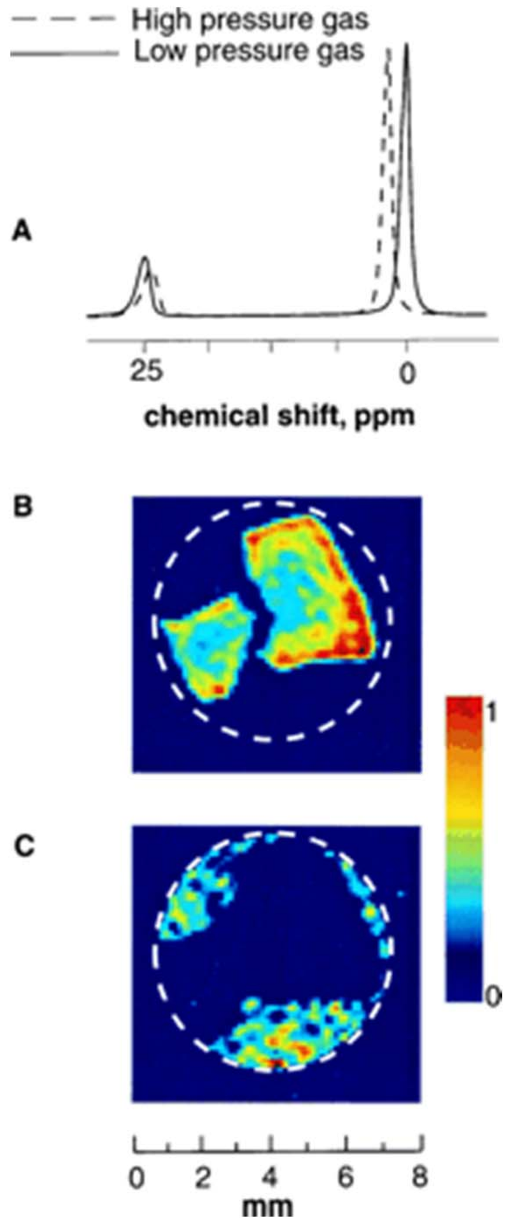
- Flow visualization: Liquids



Nuclear Magnetic Resonance Measurement of Oil and Water Distributions in Spontaneous Imbibition Process in Tight Oil Reservoirs
https://doi.org/10.3390/en11113114

NMR Visualization

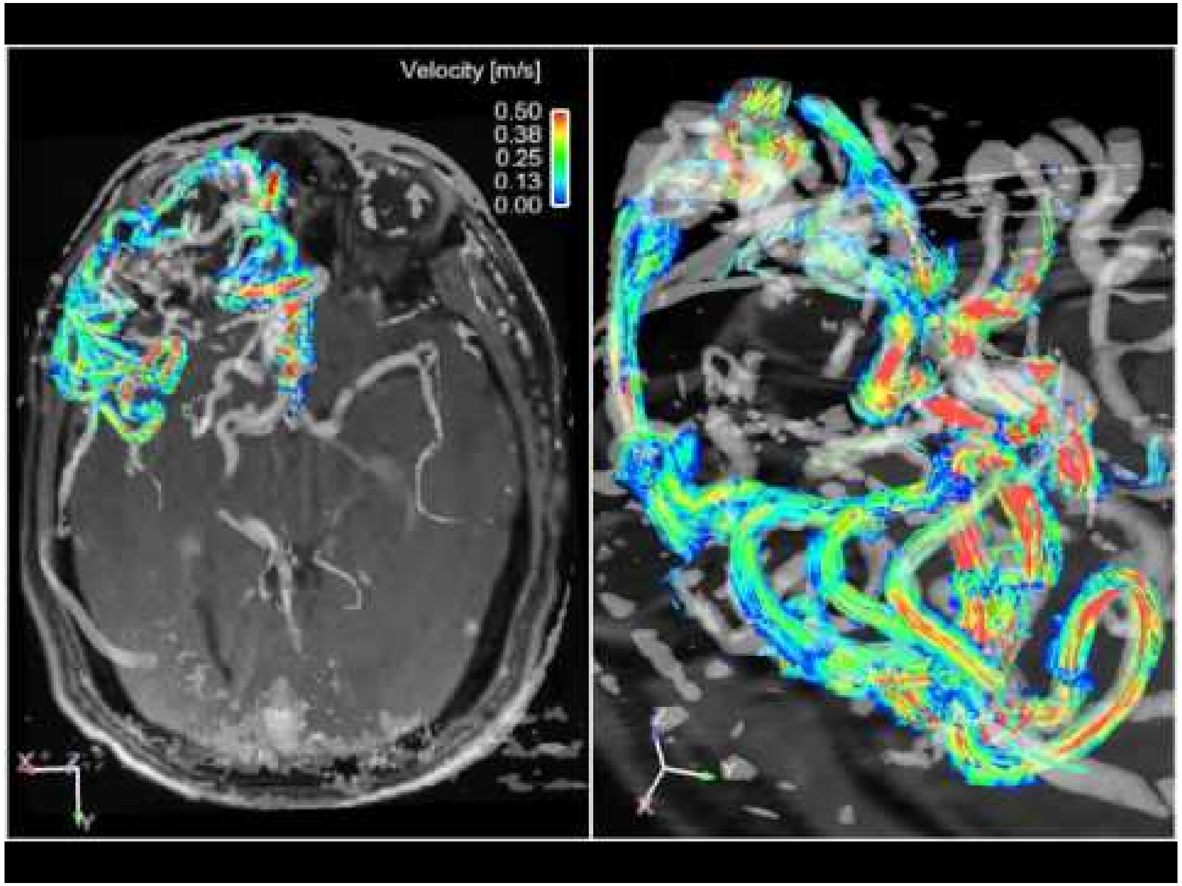
- Flow visualization: Gases
  - Gas flow and diffusion of gas into a porous media



Visualization of gas flow and diffusion in porous media
https://doi.org/10.1073/pnas.050012497

NMR Visualization

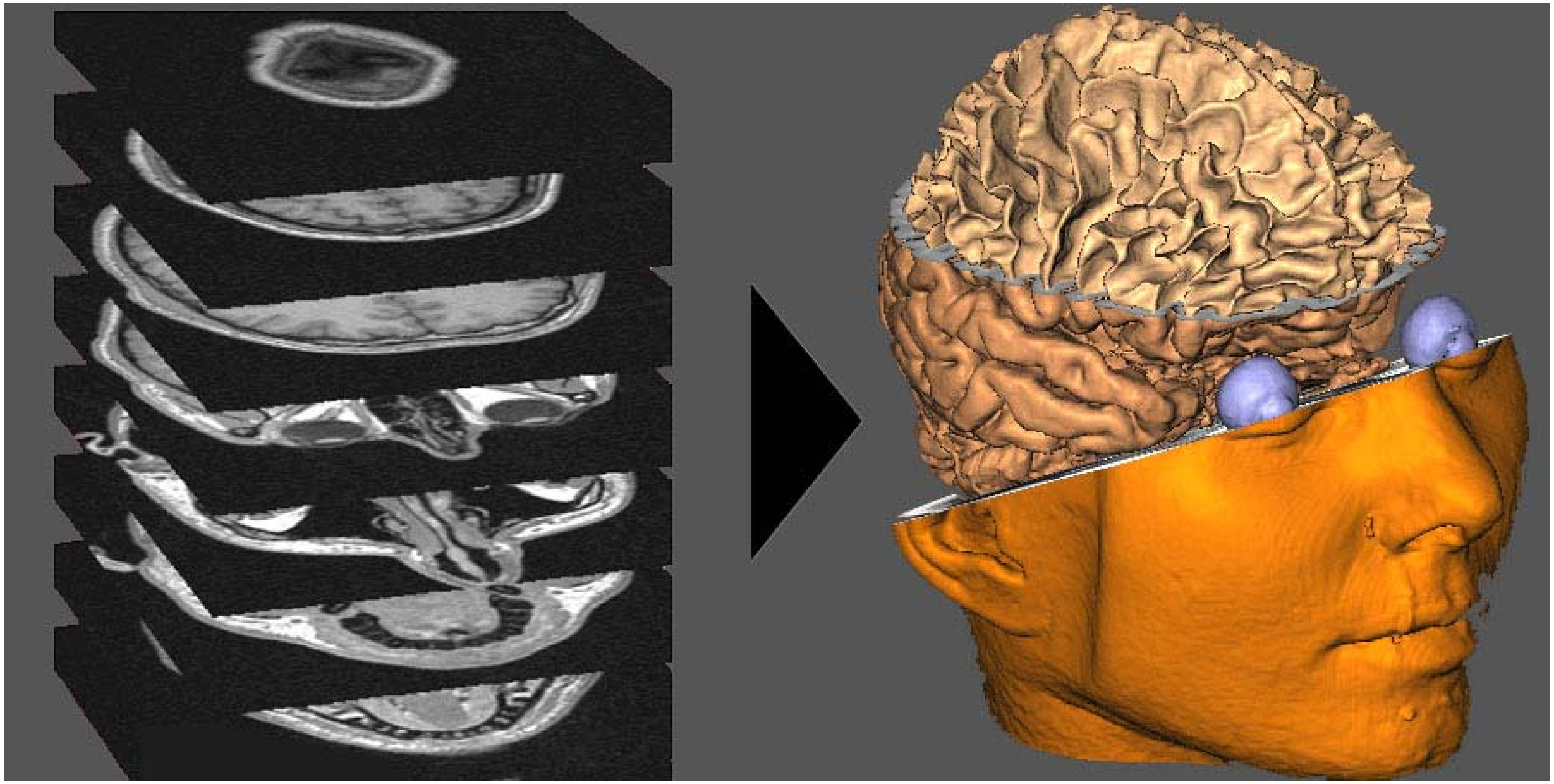
- Flow visualization: Biophysical



https://www.youtube.com/watch?v=r4ylukUKdJ8

NMR Visualization

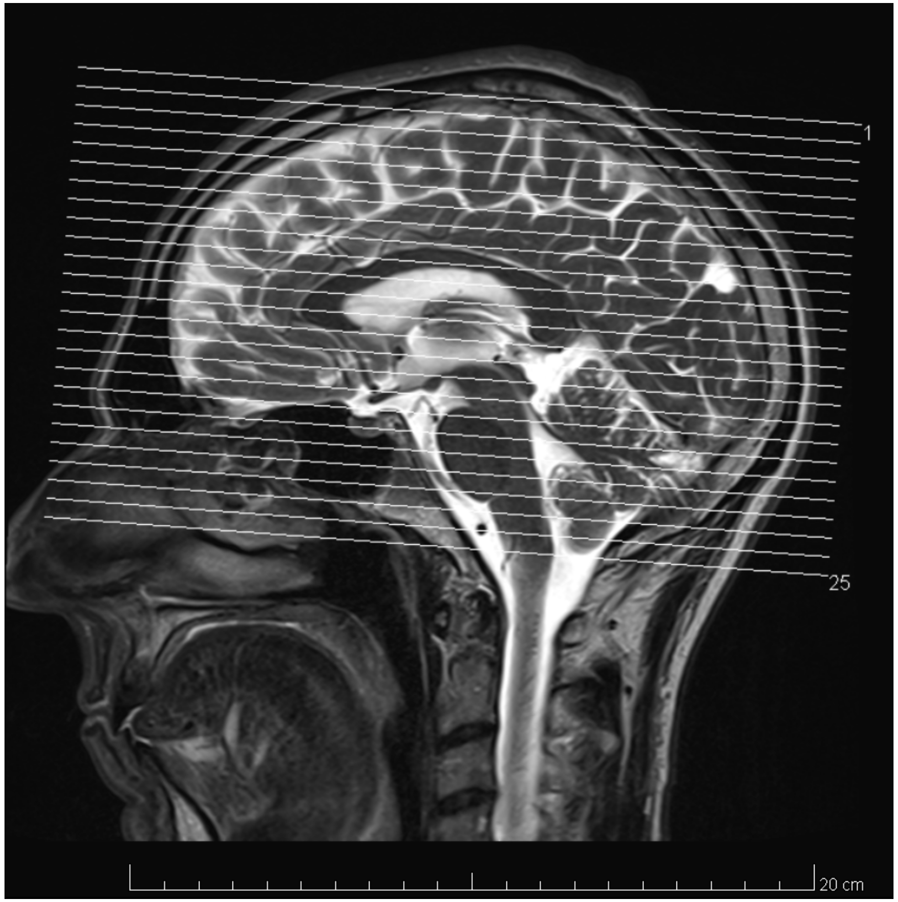
- Medical Imaging



https://www.google.de/imgres?imgurl=https%3A%2F%2Fwww.voxel-man.de%2Fmuseum%2Fweb%2F3d-prinzip.jpg&imgrefurl=https%3A%2F%2Fwww.voxel-man.de%2Fmuseum%2Fweb%2Fbs-main.html&tbnid=c8nLXDHDEuaasM&vet=12ahUKEwi0yNic1JD0AhXb7rsIHUOlAVgQMygNegUIARDZAQ..i&docid=YS-_aohEZLgzuM&w=900&h=453&q=Bild%203D%20MRT&ved=2ahUKEwi0yNic1JD0AhXb7rsIHUOlAVgQMygNegUIARDZAQ

NMR Visualization

- Visualization, Imaging, Metabolomics
- Non-invasive 2D / 3D / 4D visualization possible



Kleinpeter & Koch, J. Mol. Struc: THEOCHEM 851(1-3), 2008

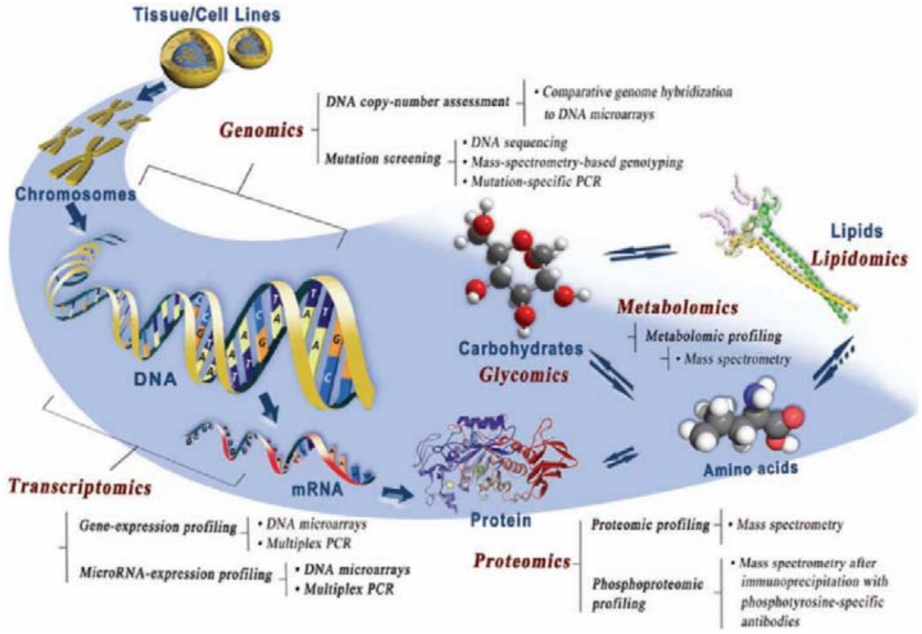
CCR, University of Buffalo, https://www.buffalo.edu/ccr/services/services/visualization/medical---scientific-visualization/nmr-shielding.html

Fuchs et al., Plant Physiology, 2, 2013

Private...

Metabolomics

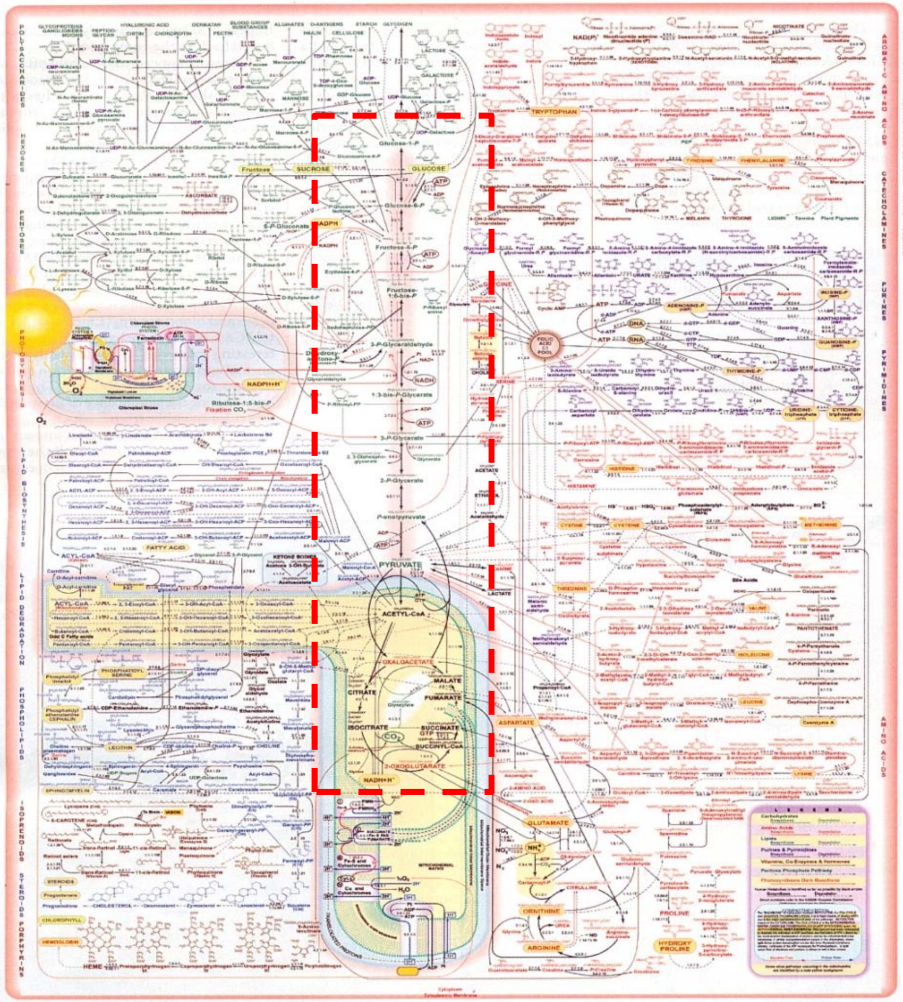
- In-situ and in vivo measurements
- Metabolomics is concerned with metabolism (of single cells, organs, or complete animals)
- ‘Omics’ sciences attempt to measure ALL chemical entities at a given level of biology
- Genomics
  - The cellular genetic potential
- Transcriptomics
  - The future direction of cellular activity
- Proteomics
  - The cellular functional potential
- Metabolomics
  - The current and actual state of the cell

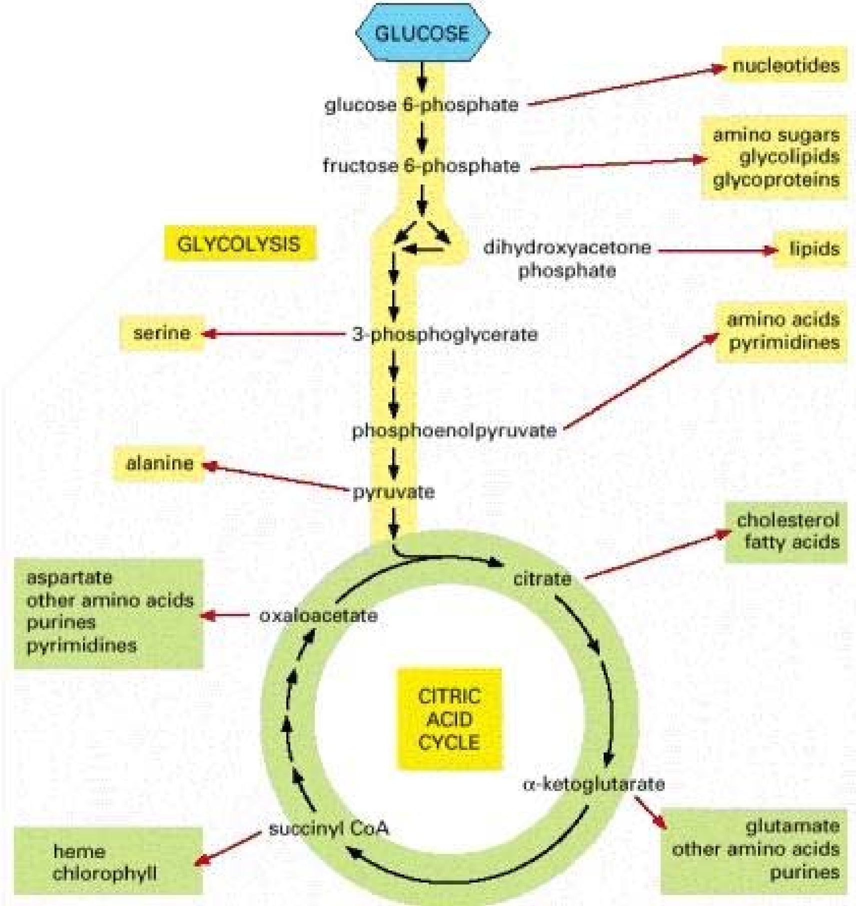


Wu, R.Q., et al., *J. Dent. Res.* 90 (2011) 561.

Metabolomics

- The metabolomics network is strongly interconnected.

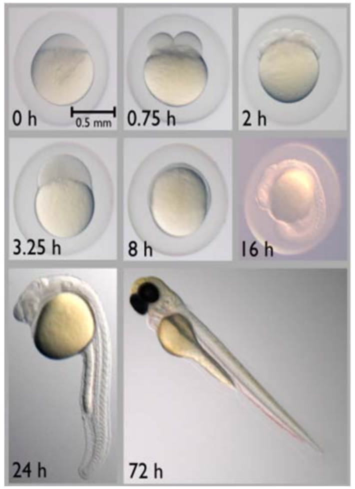




Monitoring changes in metabolite levels and/or fluxes yields information on global response to external stress

Metabolomics

- Contribution of (micro) NMR to metabolomics:
- Challenging systems require specialized hardware:
  - Small sample quantities
  - Tissue biopsy, rare biological fluids (e.g. CSF)
  - Active biological systems
  - Model organisms must be small (e.g. D. rerio, C. elegans, D. melanogaster)



0.80 mm

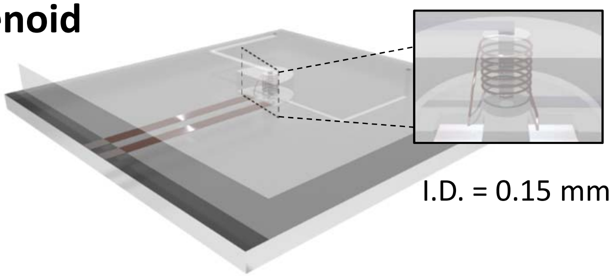
1 mm

2.5 mm

Custom MR detectors for biological samples

- Various MR detector geometries are used as dictated by the application

Solenoid

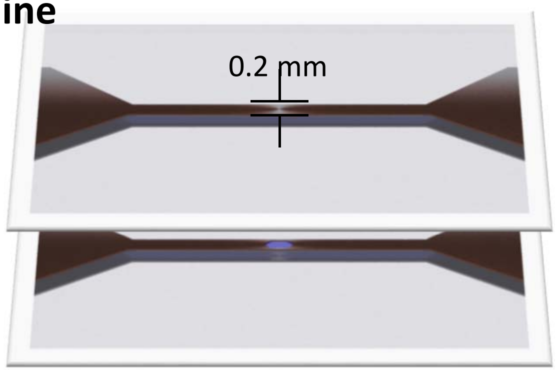


Robert Ch. Meier, et al.,
J. Micromech. Microeng. 24 (2014) 045021

Saddle

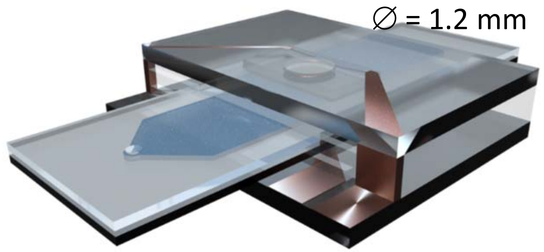
Nan Wang, et al., in progress

Stripline



Nayancee Pandey, et al., in progress

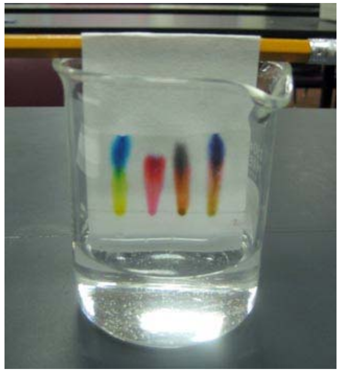
Helmholtz



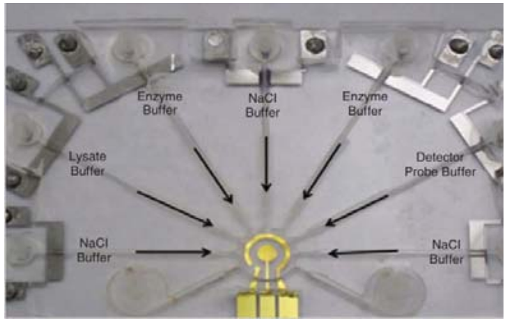
Nils Spengler, et al., PLoS ONE 11 (2016) e0146384

High-res In-situ Analysis: Hyphenation

- Microtechnology allows integrated functionalities
  - Optical microscopy
  - Chromatography
    - LC, capLC
    - HPLC, capHPLC
    - capElectrophoresis
      capIsotachophoresis
    - GC
  - Microfluidics

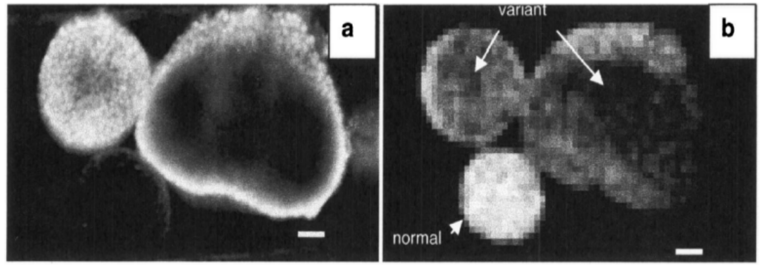


http://www.headwallphotonics.com/hs-fs/hub/145999/file-20854845-jpg/images/microscopy_banner.jpg?t=1477487927980
http://lifesciences.ieee.org/articles/316-integrated-microfluidic-systems-for-molecular-diagnostics



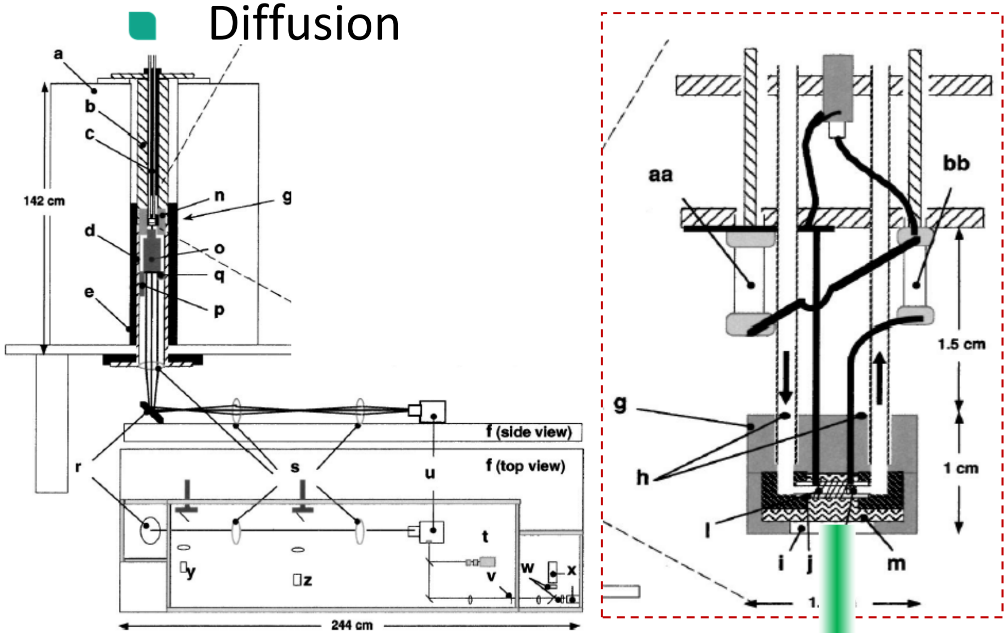
Co-registration of optical and MRI images

- High resolution optical images complemented by MRI images with different contrast
  - Optical microscopy
  - T1/T2
  - Proton density
  - Diffusion



Optical **MRI**

Diffusion contrast MRI highlights normal tissue, while optical microscopy highlights non-normal tissue



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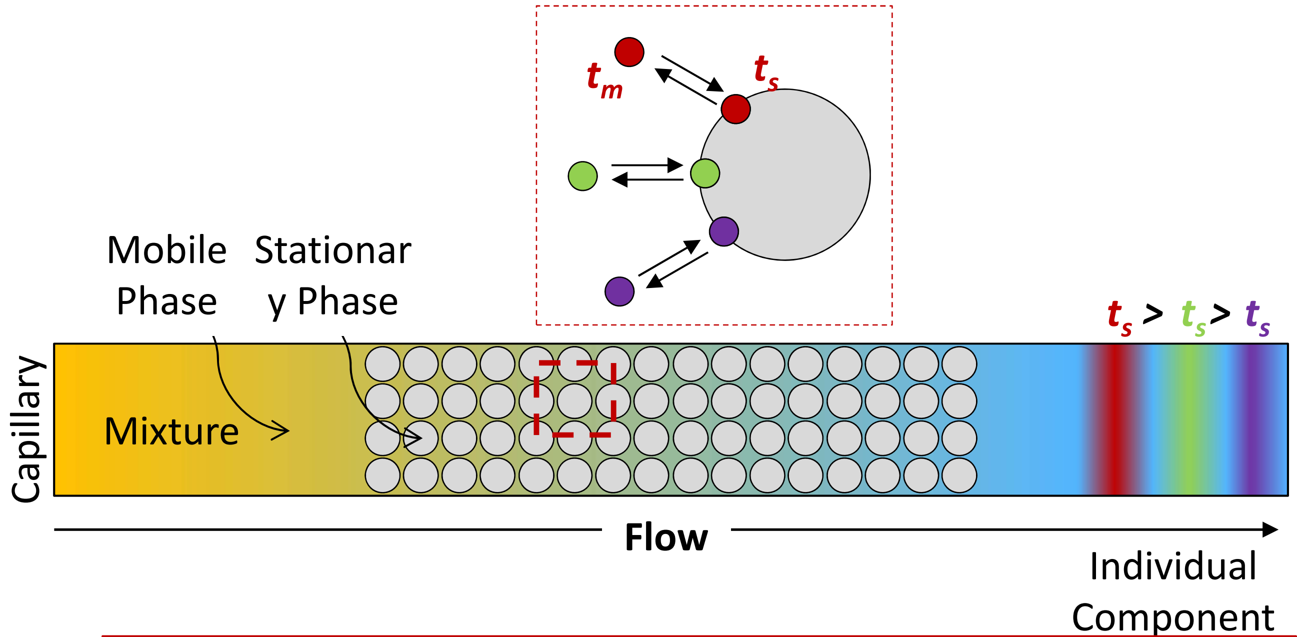
Chromatography

- Separation of a mixture by passing it through a medium in which the components move at different rates.



Purified individual components will give simplified NMR spectra!

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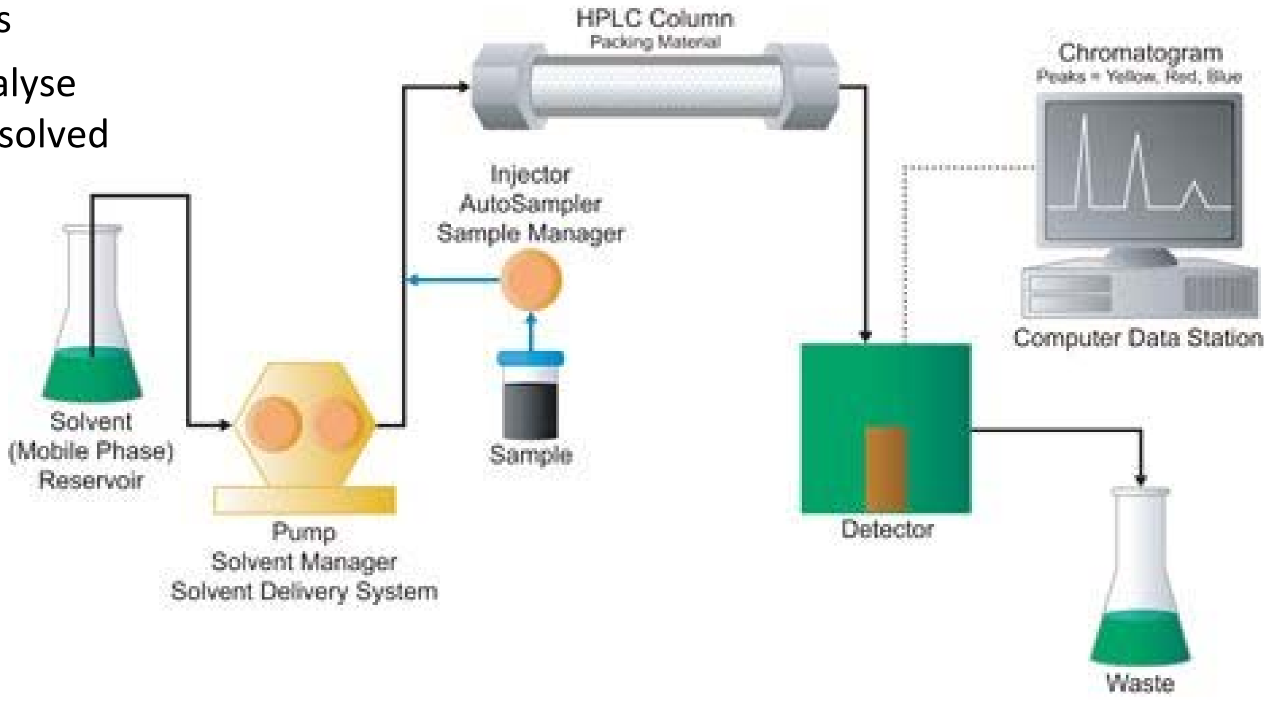
High-performance Liquid Chromatography HPLC

- **Pro's**
  - standard, relatively easy to perform
  - many libraries commercially available
  - many columns commercially available
- **Con's**
  - slow, major efforts
  - only liquids to analyse (solids have to be solved somehow)
  - expensive



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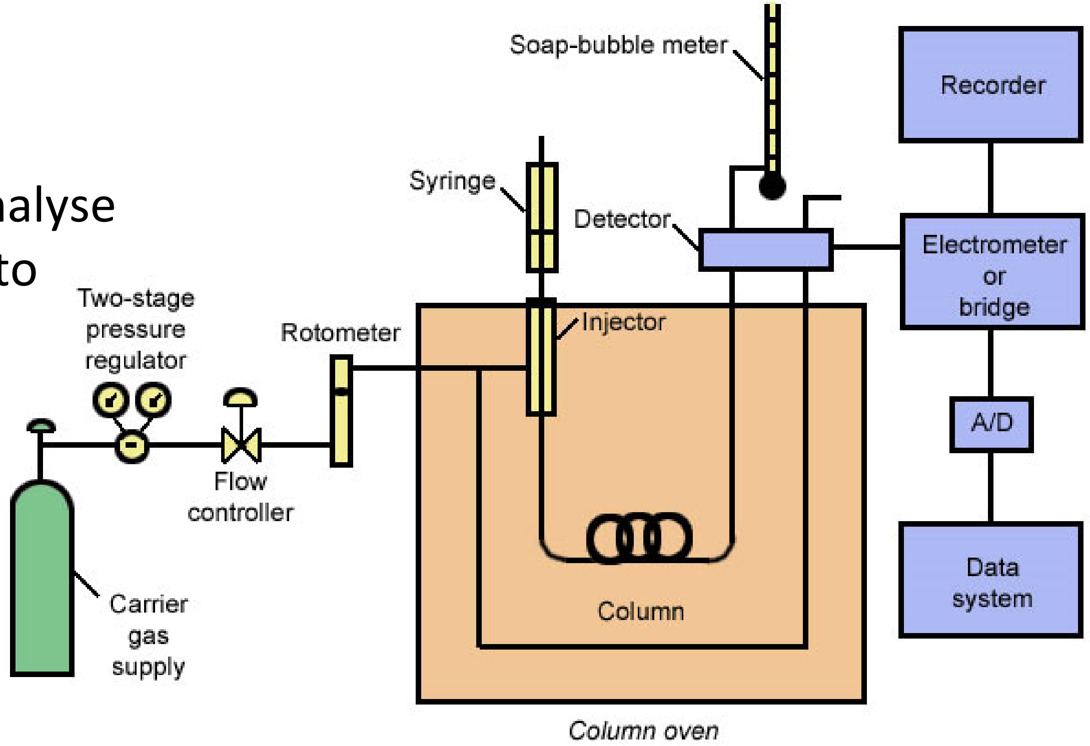
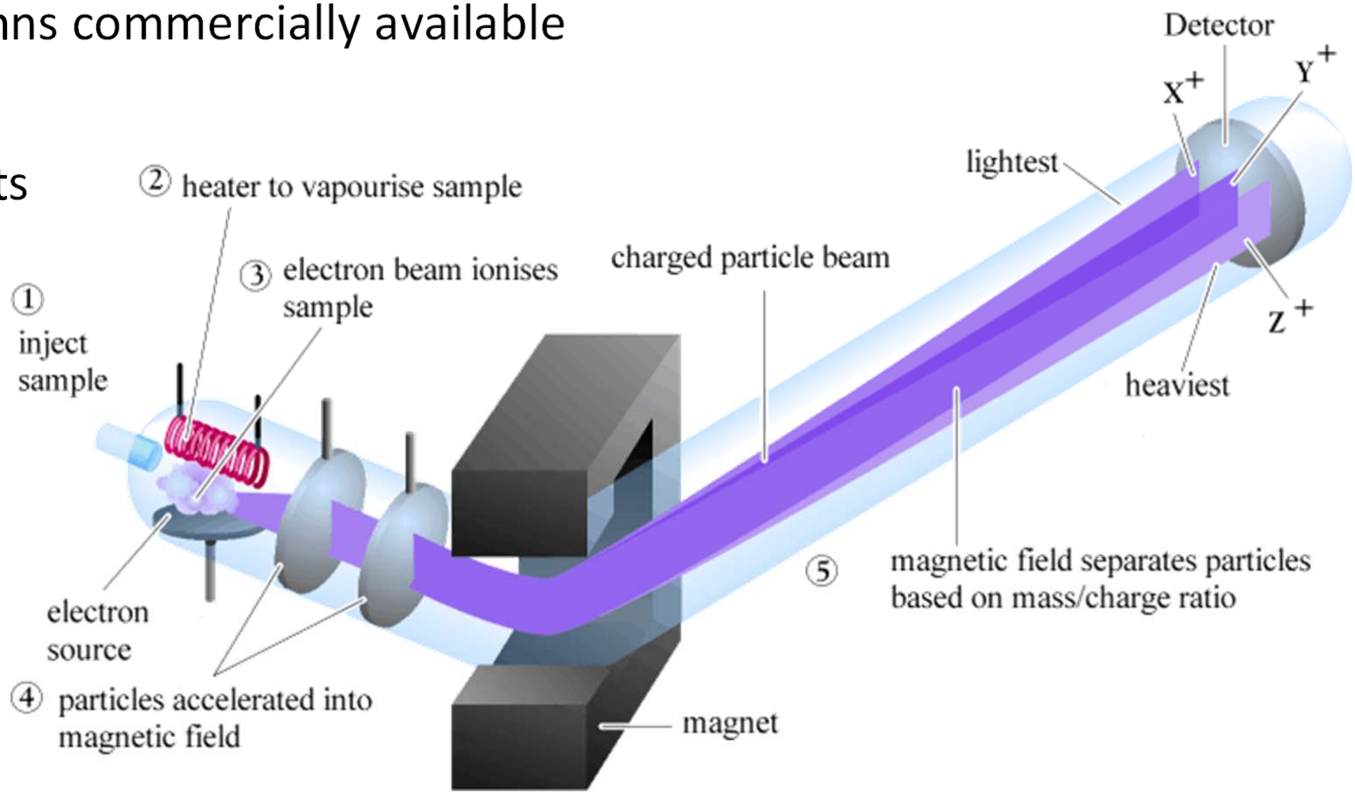
Gas Chromatography GC

- **Pro‘s**
  - standard, relatively easy to perform
  - many libraries commercially available
  - many columns commercially available
- **Con‘s**
  - slow, major efforts
  - only gases / sprays to analyse (liquids and solids have to be solved and prepared accordingly)
  - expensive



Mass Spectrometry MS

- **Pro's**
  - standard, relatively easy to perform
  - many libraries commercially available
  - many columns commercially available
- **Con's**
  - major efforts
  - expensive



Combination: GC-MS

- **Pro‘s**
  - standard, relatively easy to perform
  - many libraries commercially available
  - many columns commercially available
- **Con‘s**
  - major efforts
  - EXPENSIVE!!!!

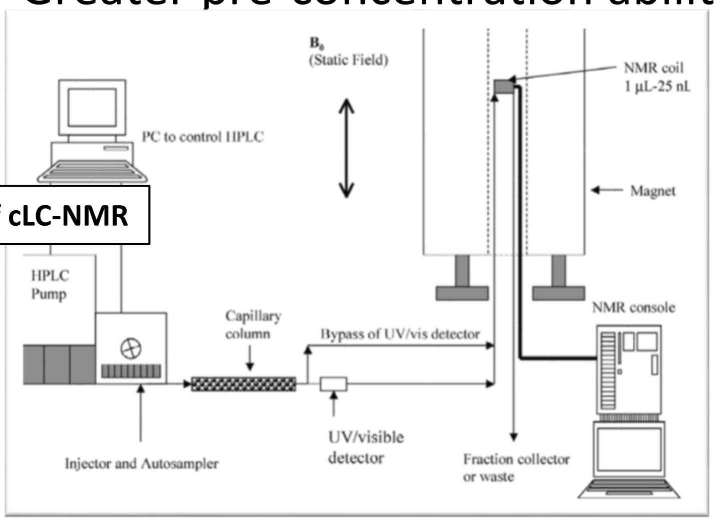
Online Chromatography

- Microtechnology allows integrated functionalities
  - Optical microscopy
  - Chromatography
    - LC, cap-LC
    - HPLC, cap-HPLC
    - cap-Electrophoresis
      cap-Isotachophoresis
    - GC
  - Microfluidics

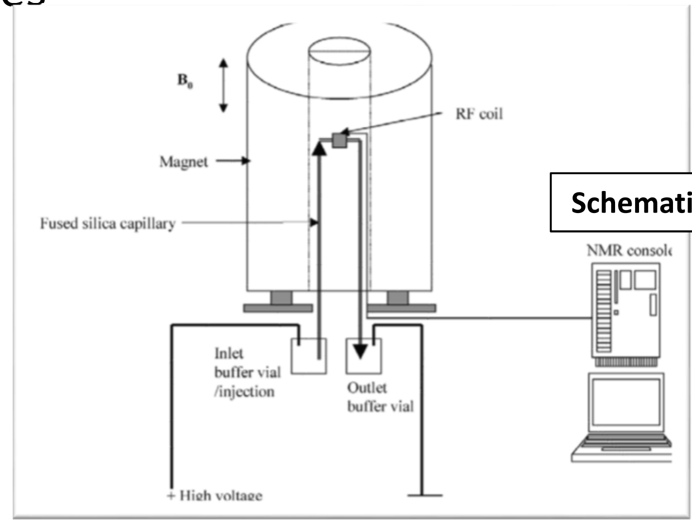
High-res In-situ Analysis: Hyphenation

- Microcoils allow for capillary-based chromatographies (cap-HPLC etc)
  - Smaller samples
  - Better separation efficiency
  - Faster analysis times
  - Greater pre-concentration abilities

Schematic of cLC-NMR



Schematic of CE-NMR



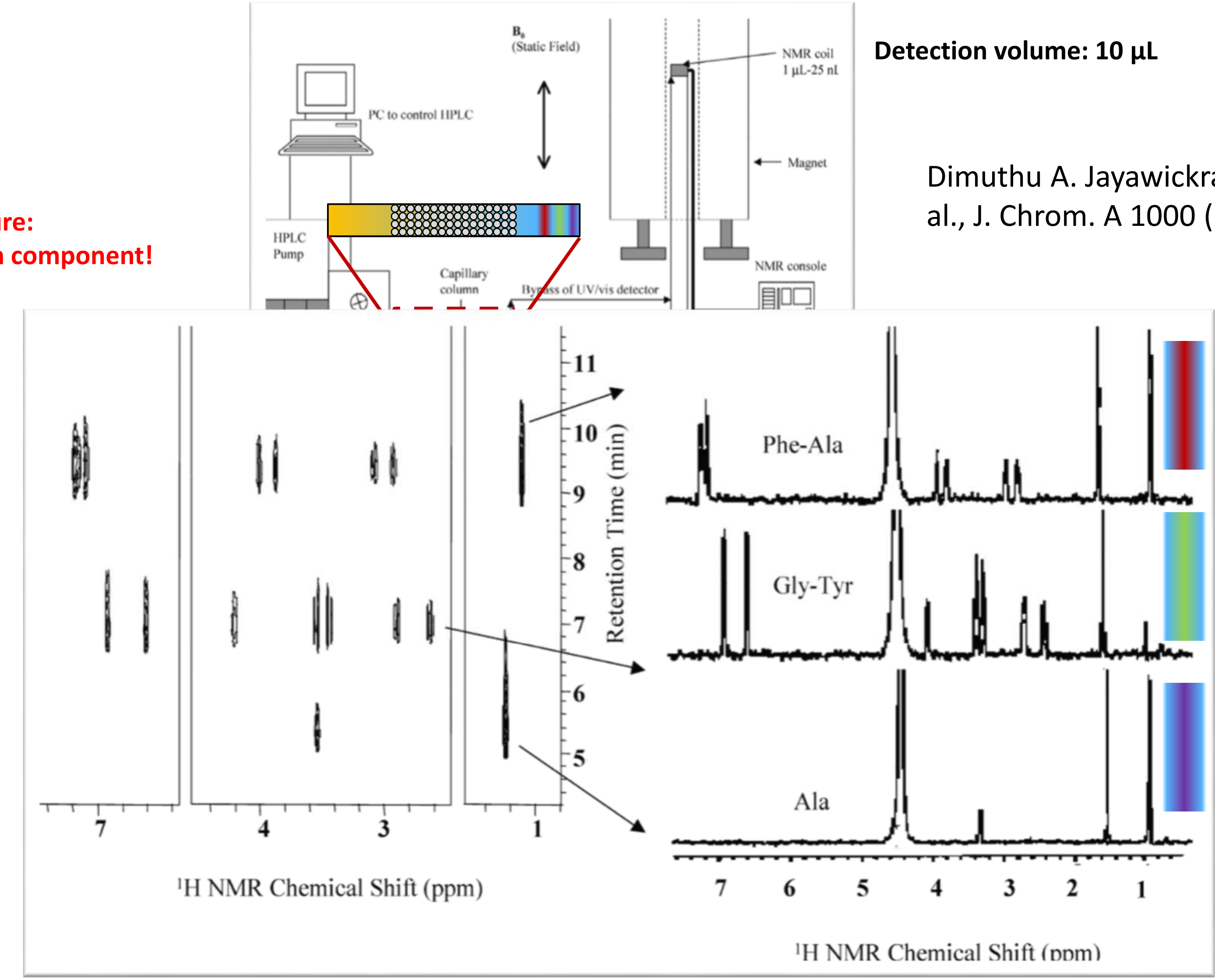
- Important in pharmaceutical sciences, natural product chemistry, and biomedical research

Separation of small peptides with on-line NMR detection

Detection volume: 10 µL

Dimuthu A. Jayawickrama, et al., J. Chrom. A 1000 (2003) 819

Sample mixture:
< 5 µg of each component!

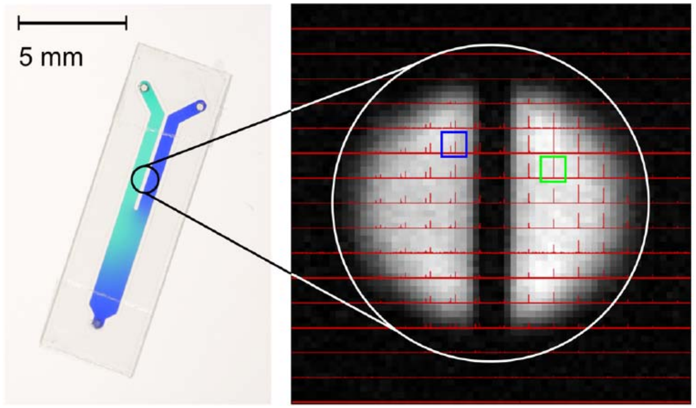


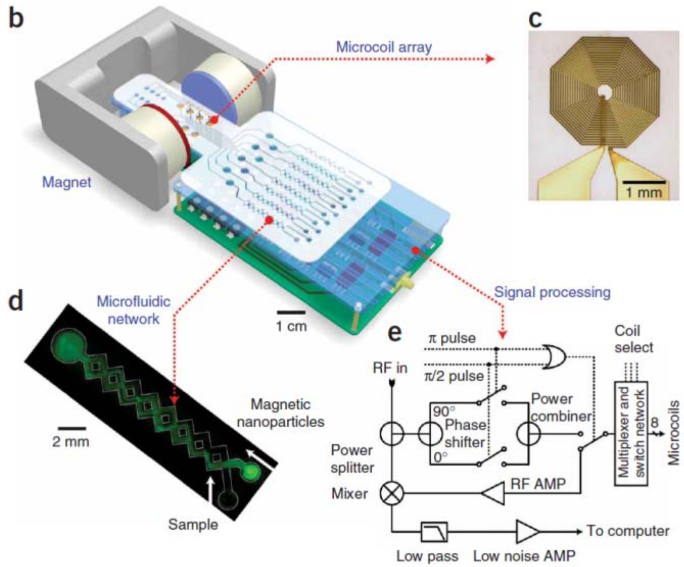
Microfluidic Integration

Karlsruhe Institute of Technology

- Precise control of reagents localized close to MR detector
  - Low reagent use
  - Monitor fast kinetics

- Outlook
  - Further functionality incorporated into microfluidic devices has yet to be fully exploited
    - T sensing
    - pH monitoring
    - Precise light delivery



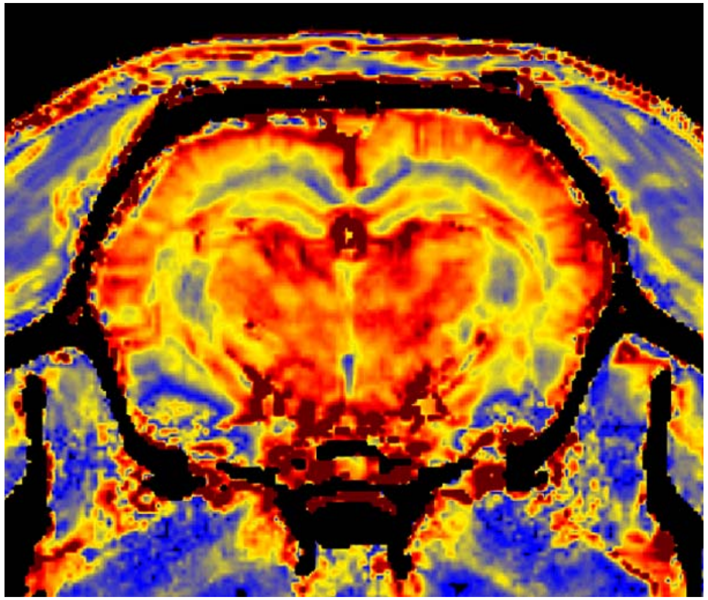


Hakho Lee, et al., Nat Med 14 (2008) 869
Nils Spengler, et al., PLoS ONE 11 (2016) e0146384

Process Measurements in µ-Systems

- NMR advantages:
  - Non-invasive (in most cases…)
  - Non-destructive
  - Relatively small efforts to bring a sample into NMR / MRI measurement
  - Well-suited for macro / mini / micro scale: ***Multi-scale approach***
  - High spatial / time resolution possible
  - Multi-measurement system: several parameters can be measured with the same technology within a short time

http://scimondo.de/1023/mrt-untersuchung-zeigt-autoantikoerper-schaedigen-auch-mikrogefaesse-im-gehirn/

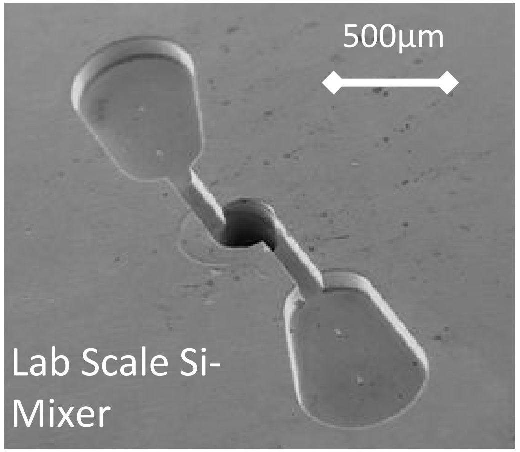


Process Measurements in µ-Systems

- NMR disadvantages:
  - Large, expensive, not easy to apply
  - Spectroscopic method, thus: Overlapping of signals!
  - Not clear yet whether low-field NMR provide good results
  - Not all materials are to be used with NMR…

Microfluidics (μ-fluidics)

- NMR disadvantages
  - Large, expensive, not easy to apply
  - Spectroscopic method, thus: Overlapping of signals!
  - Not clear yet whether low-field NMR provide good results
  - ***Not all materials are to be used with NMR…***

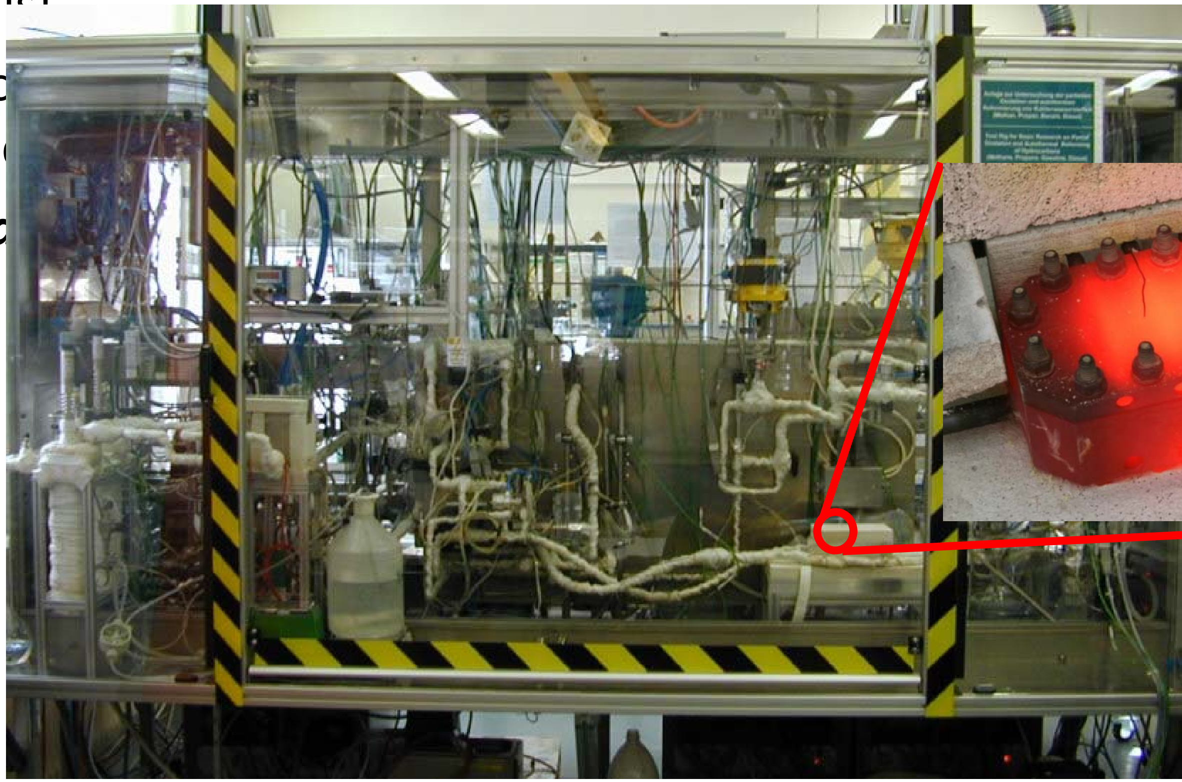


KIT– IMVT

Microfluidics (µ-fluidics)

- NMR disadvantages
  - Large, expensive, not easy to apply
  - Spectroscopic method, thus: Overlapping of signals!
  - Not c
    provi
  - ***Not c***

Lab Scale Stainless Steel Catalytic Reactor for Diesel reforming

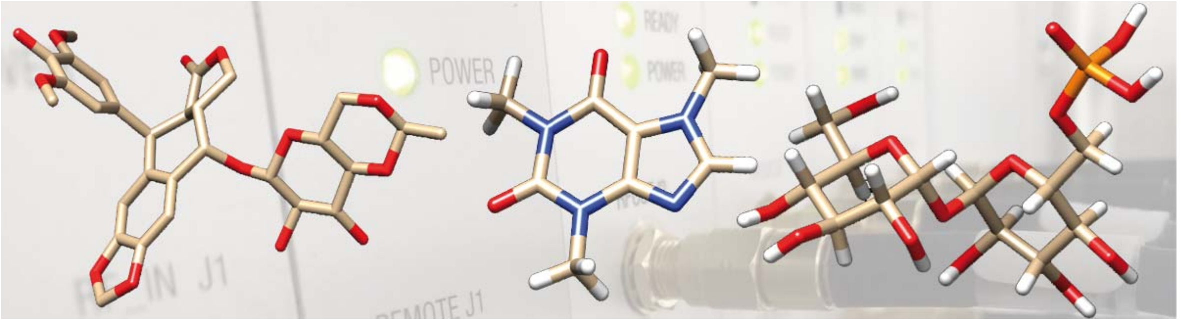


KIT– IMVT

Summary

- Learned something…
- Versatile and handy tool for different measurements
- Non-invasive, non-intrusive, non-detrimental
- Can provide several measurements “at once”
- Possibly rapid with high resolution
- Imaging in 2D and 3D possible
- Can possibly be used to obtain thermodynamical data of materials, mixtures, reactions etc.

- Has some drawbacks…



Institut für Mikrostrukturtechnik
Institute of Microstructure Technology

Finally…

Thanks for attention…

…questions?