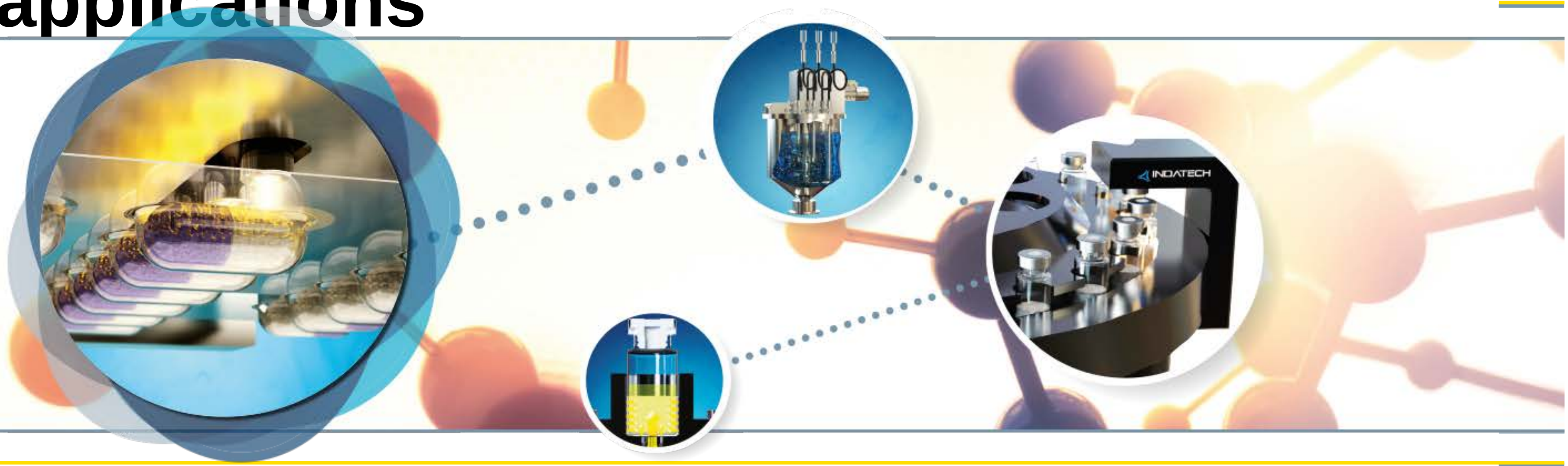
Spatially Resolved Spectroscopy & Multipoint NIR spectroscopy for in-line real-time industrial applications



IDRC 2018

Dr. Sylvie ROUSSEL sroussel@indatech.eu
Dr. Fabien CHAUCHARD fchauchard@indatech.eu

Presentation outline

- What is Spatially Resolved Spectroscopy (SRS)?
- How to use it?
  - Absorption & Scattering
  - Chemometrics tools for SAM-Spec® signal analysis
- In-line SAM-Spec® applications
  - R&D in-line tablet sorting (Servier)
  - High-speed real-time in-line tablet inspection (Proditec)
  - In-line lyo cake inspection (GEA)

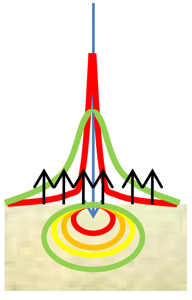
How to increase the information on a sample ?

Different ideas from different fields :

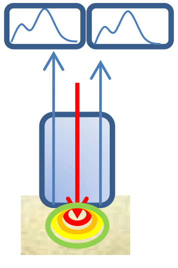
- Medicine
  - Early stage detection of carcinoma relies on physical change detection of the cell (Patterson 89).
    - Approach : perform measurements at different distances from the light source
- Study of powders (Kubelka Munk)
  - To study scattering of powder: perform measurements at different thicknesses
  - Double integrating sphere approach
- Study of liquids
  - Turbidity : measurement at different angles
- Spectral Imaging :
  - Moving a fiber along the sample to scan it

➔ What is SRS?
What is Sam-Spec® concept?

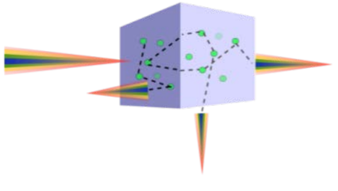
- **Getting more information by the combination of simultaneous fiber imaging measurements combining:**



- Spatially Resolved Spectroscopy (SRS) = performing spectroscopic measurements at different distances from the light source
- Different locations in reflection mode



- Different positions at same distance (homogeneity)
  - Single probe and multiprobe approach

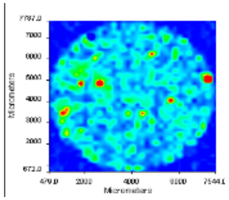


- Different angles for liquid (collimated transmission, uncollimated transmission, reflection, 90°)

Igne B, Talwar 2, Feng H, Drennen JK, Anderson CA. 2015. Near-Infrared Spatially Resolved Spectroscopy for Tablet Quality Determination. *J Pharm Sci*.;104(12):4074-4081

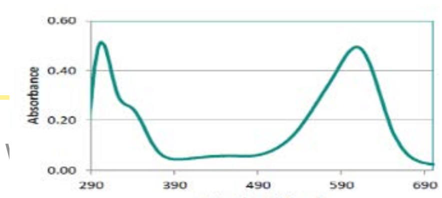
The patented SAM-Spec® solution

Hyperspectral imaging
= too high resolution



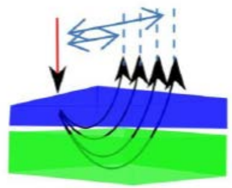
SAM-Spec® SRS
Spatial Advanced Measurement by SPECtroscopy

Single spectrum acquisition
= not enough information

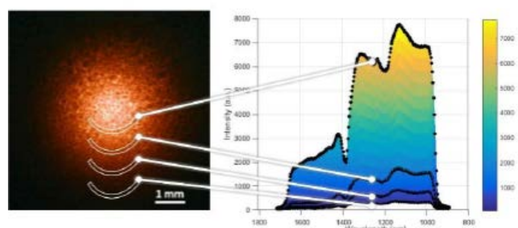


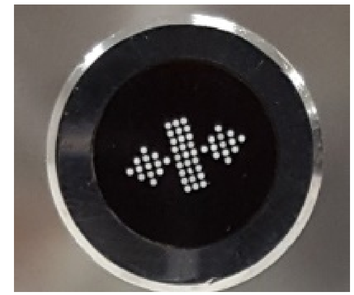
1 illumination

Several back scattered signals

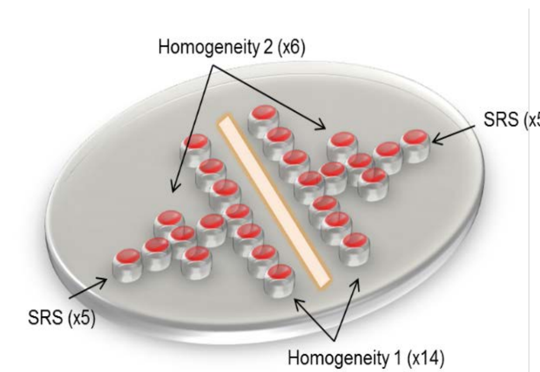


http://www.indatech.eu/en/products/probes/sam-spec.html





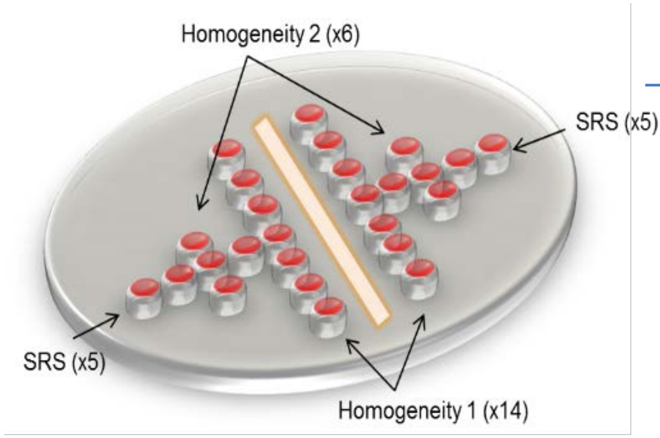
Examples of probe head



The patented SAM-Spec® solution

CHAUVIN ARNOUX INDATECH

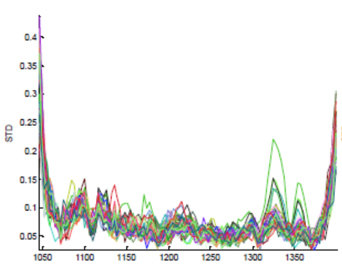
➔ More than just chemical concentration prediction



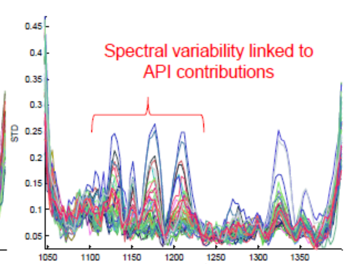
Homogeneity fibers

Standard deviation of spectra for direct information on homogeneity

STD spectra:
50 P1 tablets



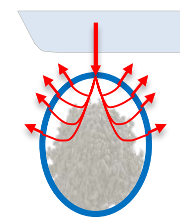
STD spectra:
50 P2 tablets



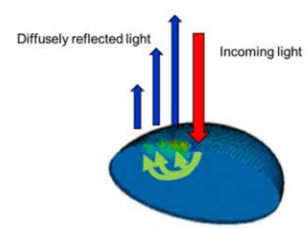
Spatially Resolved Spectroscopy (SRS) fibers (scattering information)

- Density, mean particle size, hardness

- Weight of a capsule



- Signal optimization
Select the best path of light to obtain the best prediction

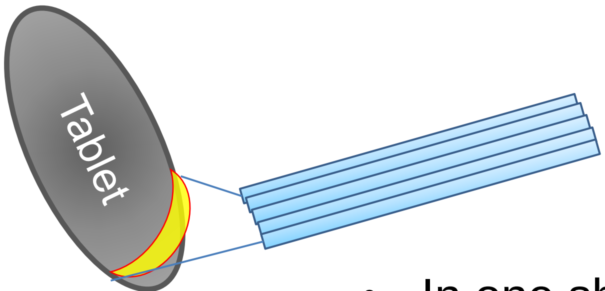


Measure up

Example of SAM-Spec® for in-line tablet measurement

How to increase the surface information ?

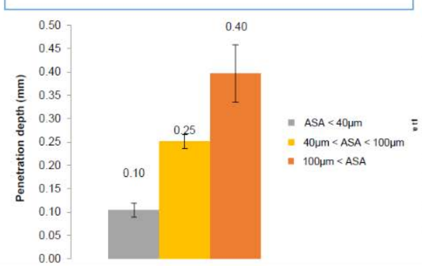
Scan of a tablet

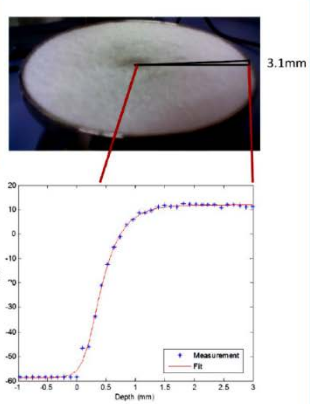


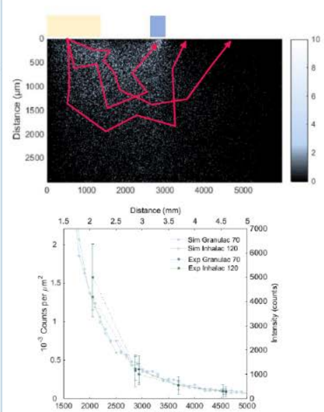
NIR : 900-1700nm
SRS probe: up to 27 simultaneous channels

- In one shot (~2 ms) on a tablet: 10 to 25 spectra
- Total: 90 to 675 spectra per tablet
- Surface and subsurface measurements

- Penetration depth is dependent on the sample and the sampling geometry.
- There is no single „depth“, in reflection the signal is coming with exponential contribution from the layers.







Scheibelhofer Otto (2016). Challenges of process analysis in continuous manufacturing, *PAT conference*, Lyon, France 2016.

Scheibelhofer O., Wahl P., Larchevêque B., Chauchard F., G. Khinast, J. (2018). Spatially Resolved Spectral Powder Analysis: Experiments and Modeling. *Applied Spectroscopy.* 72.

research center pharmaceutical engineering

Measure up

Example of SAM-Spec®
for process monitoring

How to increase the process understanding and the process performance ?

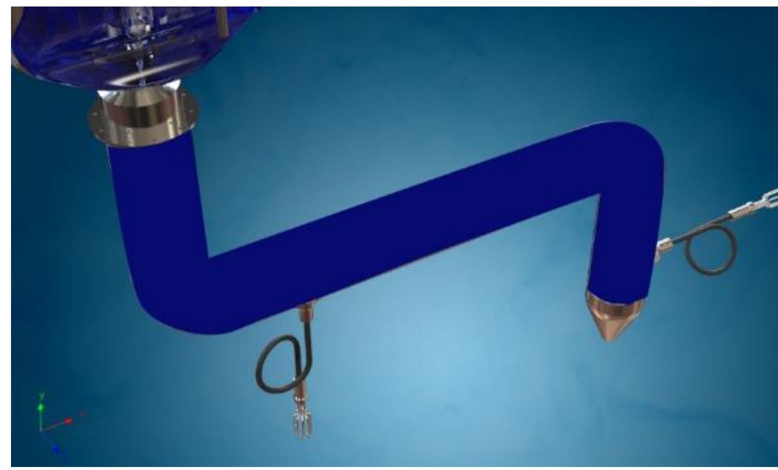
➡ Scan of different critical process steps or lanes

Reactor case

Probe 1 Probe 2 Probe 3

Local homogeneity (SRS)
+ Homogeneity at different depths (multi probes)

Continuous process



Probe 2

Probe 1

Real-time mapping of a continuous process at different locations

Presentation outline

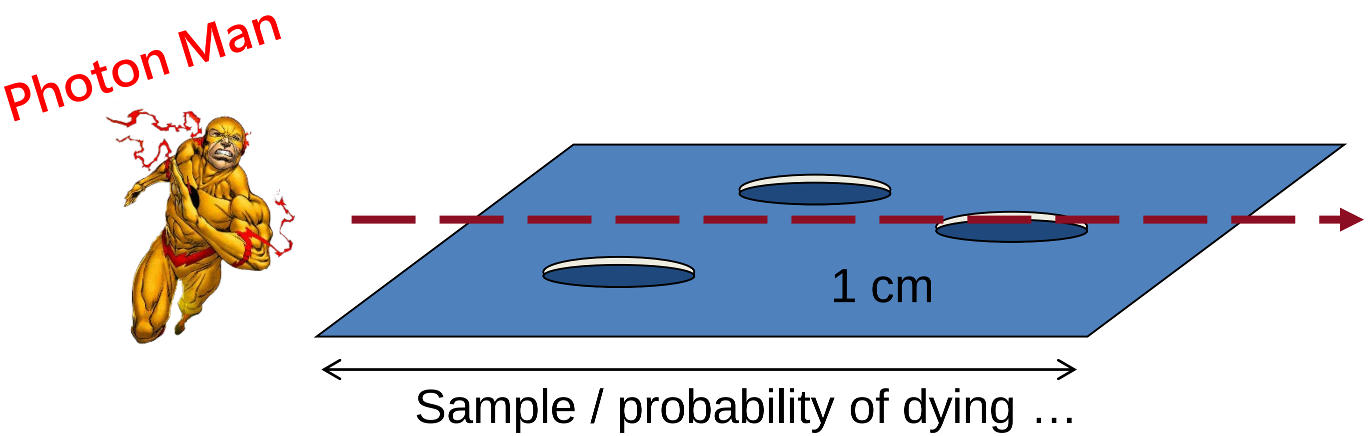
- What is Spatially Resolved Spectroscopy (SRS)?
- How to use it?
  - **Absorption & Scattering**
  - Chemometrics tools for SAM-Spec® signal analysis
- In-line SAM-Spec® applications
  - R&D in-line tablet sorting (Servier)
  - High-speed real-time in-line tablet inspection (Proditec)
  - In-line lyo cake inspection (GEA)

Absorption coefficient

- The absorption coefficient is defined as the concentration of a chemical product (c) x pure spectrum (k)

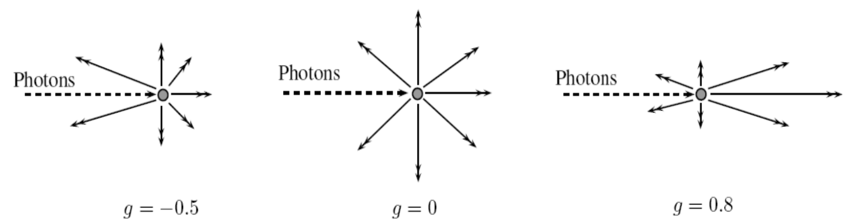
$$\mu_a(\lambda) = c.k(\lambda) \text{ in } cm^{-1}$$

- The absorption coefficient gives the probability for a photon of being absorbed per unit length

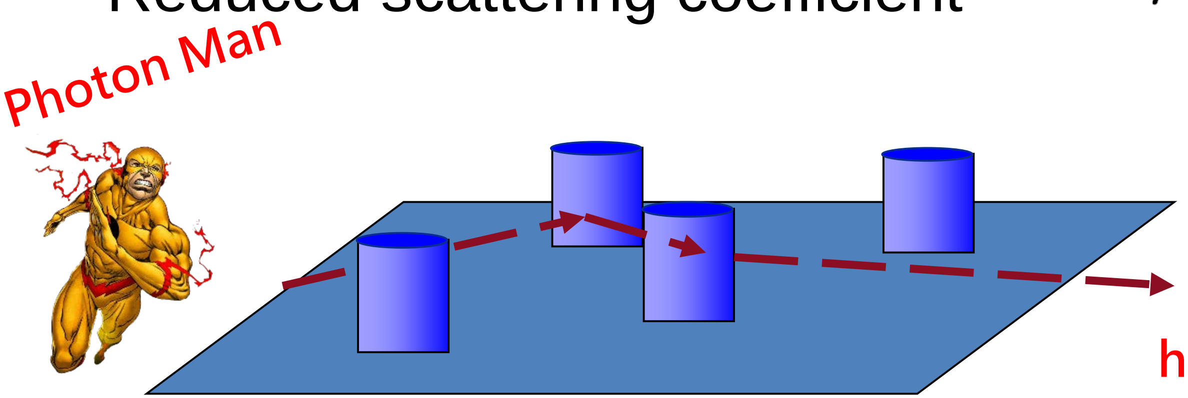


Scattering coefficient

- Scattering coefficient = probability for a photon of being scattered μ_s
- Anisotropy coefficient
  g (possible values: [-1 1])

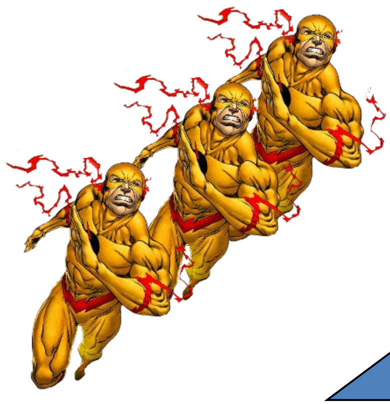


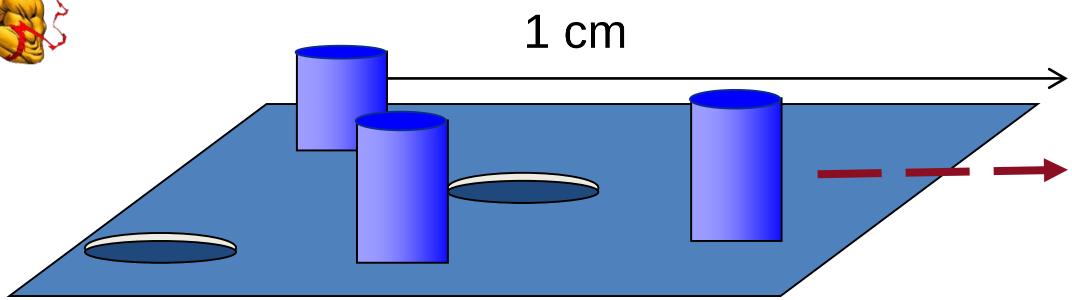
- Reduced scattering coefficient $\mu_s' = (1 - g)\mu_s$



Sample / probability of meeting point …

Equation of diffusion





Number of photons reaching the detector for

Number of photons for irradiation I_0

- Equation of Diffusion (Patterson 1989)

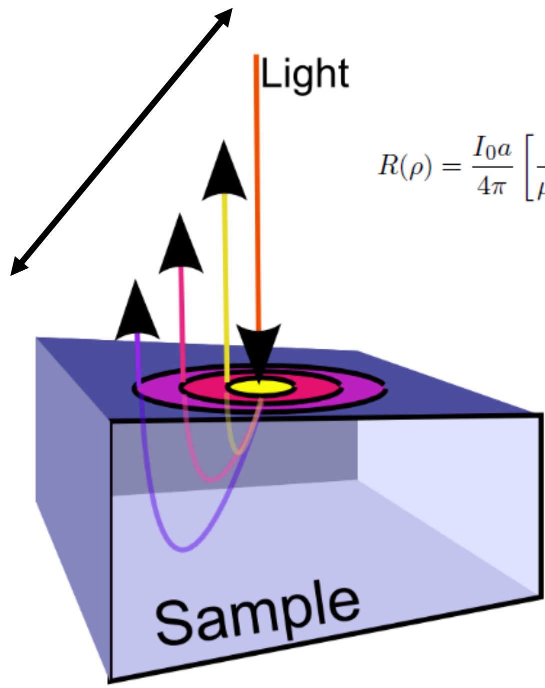
$$\frac{1}{v}\frac{\partial \phi(\mathbf{r},t)}{\partial t} - D\nabla^2\phi(\mathbf{r},t) + \mu_a\phi(\mathbf{r},t) = \frac{1}{v}Q_0(\mathbf{r},t)$$

> Different measurement positions can be used to separate physical attribute (μ_S) from chemical attribute (μ_a)

Spatially Resolved Spectroscopy (SRS)

Signal attenuation

Mean particle size
Density
Porosity
Particle shape
Coating



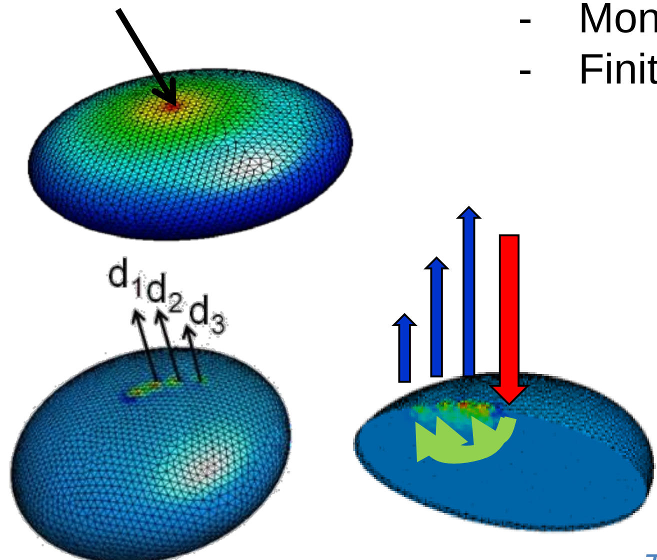
- Farnell's equation (1992)

$$R(\rho) = \frac{I_0 a}{4\pi}\left[\frac{1}{\mu_{tr}}\left(\mu_{\text{eff}} + \frac{1}{r_1}\right)\frac{\exp(-\mu_{\text{eff}} r_1)}{r_1^2} + \left(\frac{1}{\mu_{tr}} + 2z_b\right)\left(\mu_{\text{eff}} + \frac{1}{r_2}\right)\frac{\exp(-\mu_{\text{eff}} r_2)}{r_2^2}\right]$$

$$\begin{aligned}
\mu_{\text{eff}} &= [3\mu_a(\mu_a + \mu_s')]^{-1} \\
a &= \mu_s'/\mu_{tr} \\
r_1 &= [z_0^2 + \rho^2]^{1/2} \\
r_2 &= [(z_0 + 2z_b)^2 + \rho^2]^{1/2} \\
z_0 &= 1/\mu_s' \\
z_b &= 2AD
\end{aligned}$$

Simulation example

Irradiation



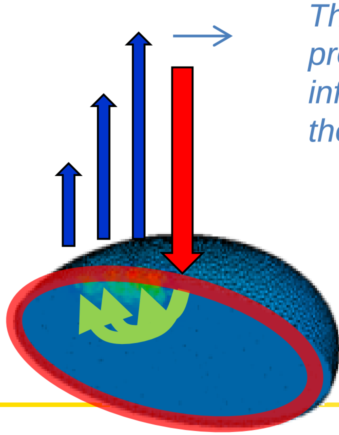
Various simulation tools exist:

- Monte Carlo simulation
- Finite Element Method (NIRFAST)

NIRFAST

http://www.dartmouth.edu/~nir/nirfast/

Pr. Hamid Dehghani



The first position provides more information from the coating

Drawbacks of simulations:

- μ_a and μ_s independence hypothesis
- Boundary conditions usually unknown
- Optical properties of all compounds
- Even more complex with heterogeneous samples
- Computation time

Coating

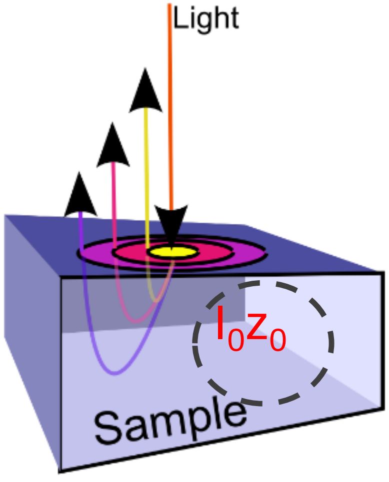
Presentation outline

- What is Spatially Resolved Spectroscopy (SRS)?
- How to use it?
  - Absorption & Scattering
  - **Chemometrics tools for SAM-Spec® signal analysis**
- In-line SAM-Spec® applications
  - R&D in-line tablet sorting (Servier)
  - High-speed real-time in-line tablet inspection (Proditec)
  - In-line lyo cake inspection (GEA)

Chemometrics tools for SAM-Spec® signal analysis

1. Robustness / Reference
2. Measurement distance optimization
3. Prediction validity
4. Homogeneity / Dosage uniformity
5. Mean particle size / Density / Hardness

1. Robustness / Reference

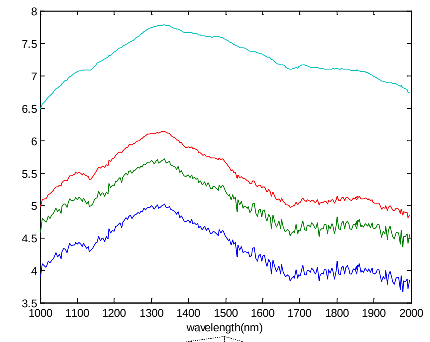


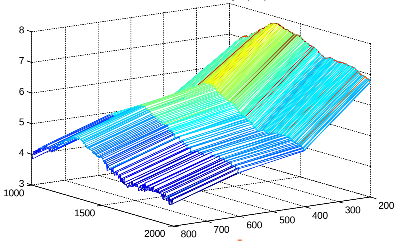
- Light reference measurement into the sample (or into the process)
  - With a classical probe, it is necessary to perform a reference / spectralon measurement
  - With SRS : $R(\rho) = I_0 z_0 \frac{\exp(-\mu_{eff}\rho)}{2\pi\rho^2}\left(\mu_{eff} + \frac{1}{\rho}\right)$

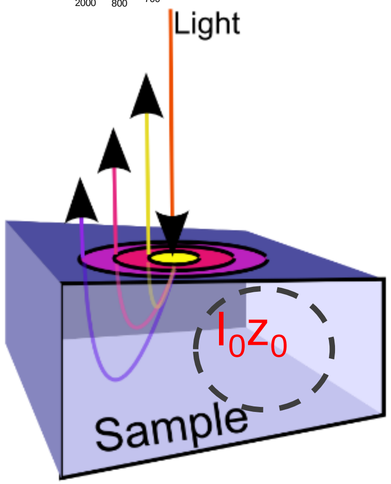
$$z_0 = 1/\mu_s'$$
$$\mu_{\text{eff}} = \left[3\mu_a(\mu_a + \mu_s')\right]^{-1}$$

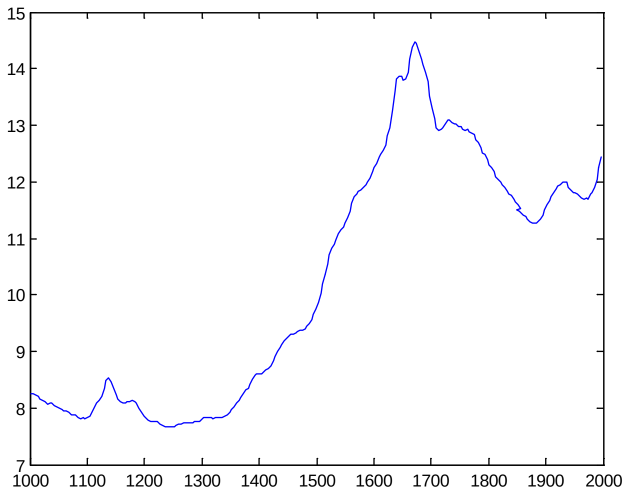
➔ A ratio of 2 spectra at 2 different locations removes the effect of the light source fluctuation and the major part of the scattering effect

Ex : No reference needed

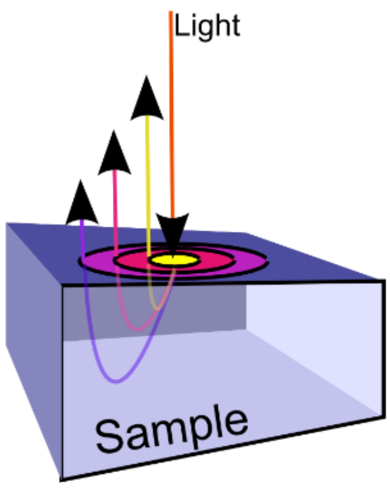








2. Optimal measurement distance



Different distances and depths into the sample

- The measurements at different locations provide different light pathlengths and depths into the sample

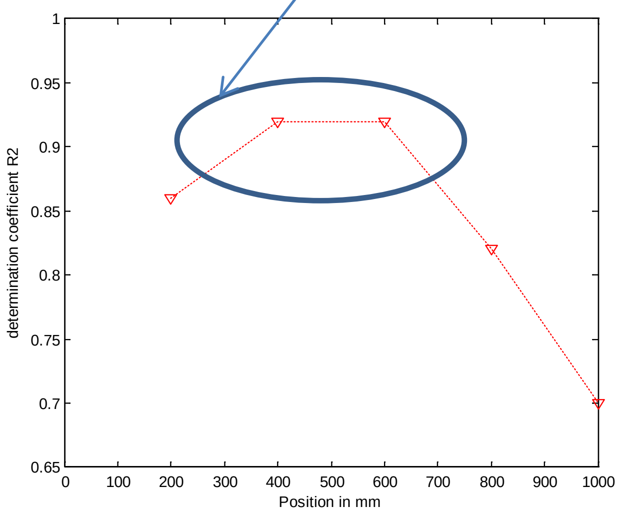
➔ Select the best distance from the illumination point to get the best back-scattered information

1. Perform a measurement with all channels
2. Derive calibration models based on each channel
3. Evaluate each calibration performance depending on the distance
4. Select the ideal probe configuration

2. Optimal measurement distance

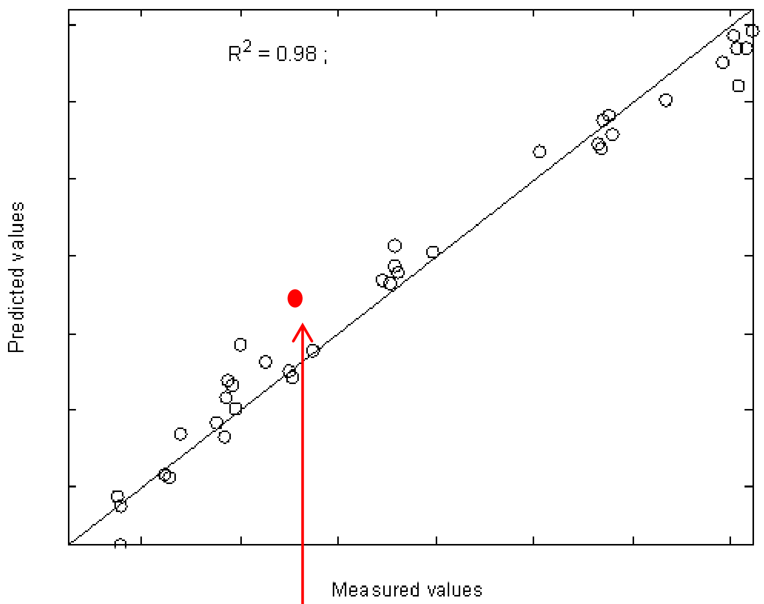
- Ex: measurement optimization for flour protein prediction

Optimal distance



This optimization is highly interesting for low concentration predictions or low density products such as fluid bed drying

3. Validity of prediction



- Since several measurements and models can be used, several predictions can be performed for one sample

➔ Several predictions (different locations and models)

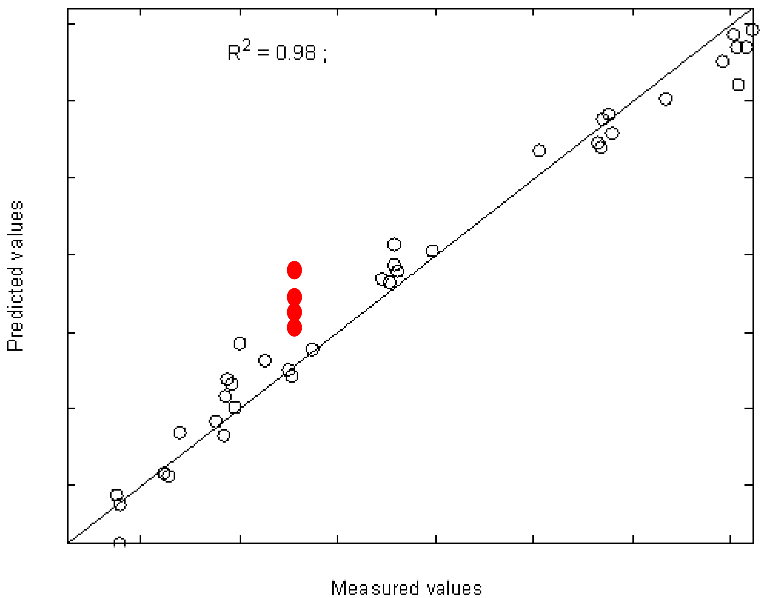
➔ Data fusion

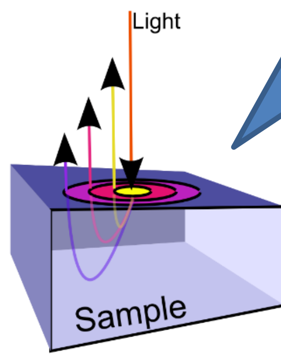
➔ Confidence interval and statistical tools to assess the validity of prediction

What is the prediction uncertainty ?
In-line, there is no other information than the PLS predicted value

3. Validity of prediction

With SRS measurements, several predictions

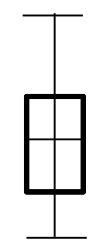




Set of spectra
Set of prediction

Inline/ Online diagnostic on the prediction

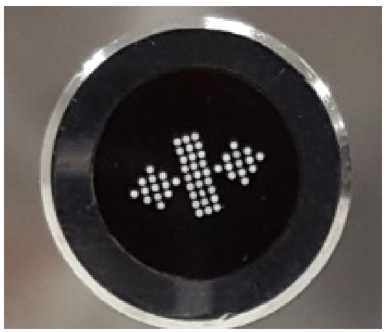
Standard deviation
Mean of prediction



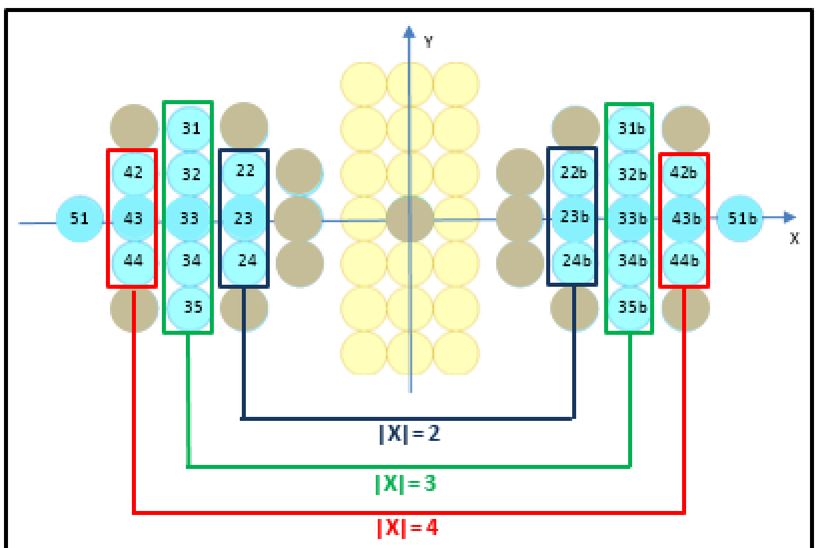
PCA on the spectra
Residual analysis

4. Homogeneity & Uniformity

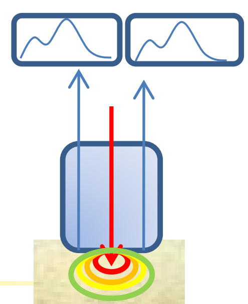
- Homogeneity : standard deviation between signals from fibers at the same distance / illumination



- 3 std spectra are computed
- Each one is the standard deviation of spectra at different distances from y
  - X=2 : std on 6 spectra
  - X=3 : std on 10 spectra
  - X=4 std on 6 spectra



When X increases, the analyzed volume and measurement depth increase



4. Homogeneity index Definition

- Homogeneity spectrum: S_k is calculated with n spectra at distance x = K ➔ X_k

$$S_k = \sqrt{\frac{(X_k - \overline{X_k})^2}{n-1}}$$

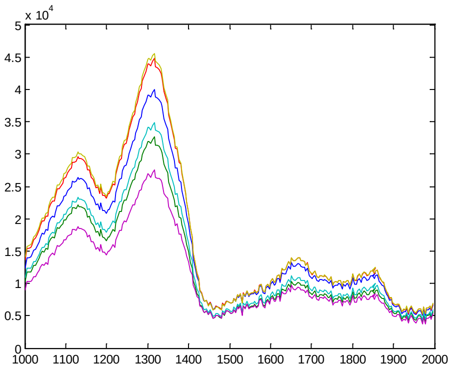
➔ For more details: M. Boiret, F. Chauchard, 2017. Use of near infrared spectroscopy and multipoint measurements for quality control of pharmaceutical drug products, *Analytical & Bioanalytical Chemistry,* 409(3):683-691.

- The homogeneity index is calculated based on the following steps:
  - Spectroscopic preprocessing
  - Standard deviation calculation

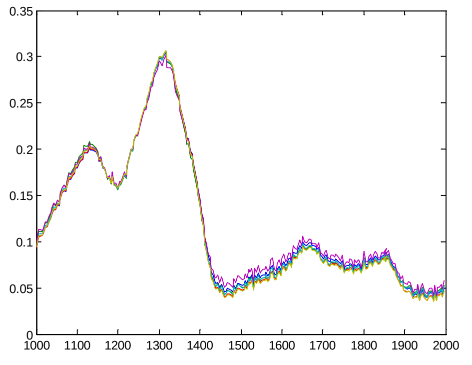
- The homogeneity index can be then used with SIMCA, PLS, MSPC (continuous process), BSPC (batch modelling)…

4. Homogeneity example

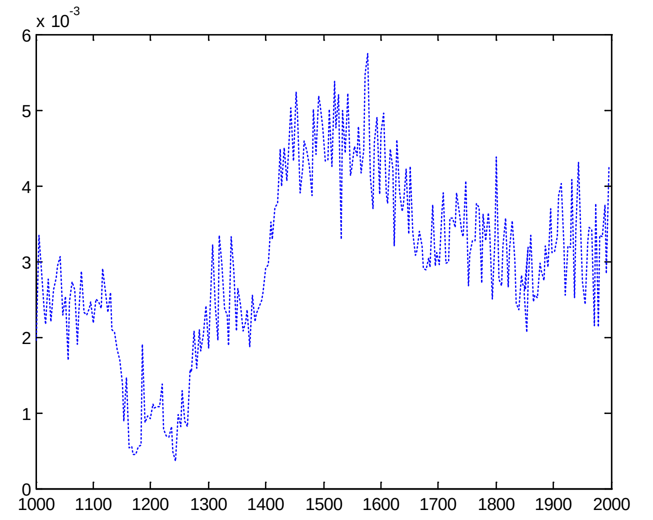
- Flour measurement
- 6 channels are measured at the same distance



Raw spectra



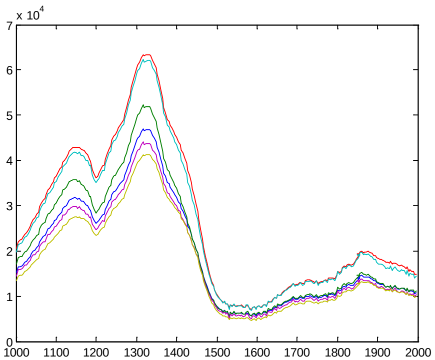
Normalized spectra



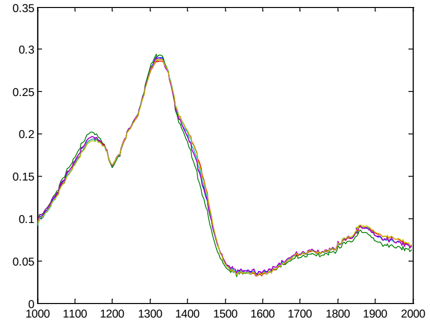
Std(normalize(x))

4. Homogeneity example

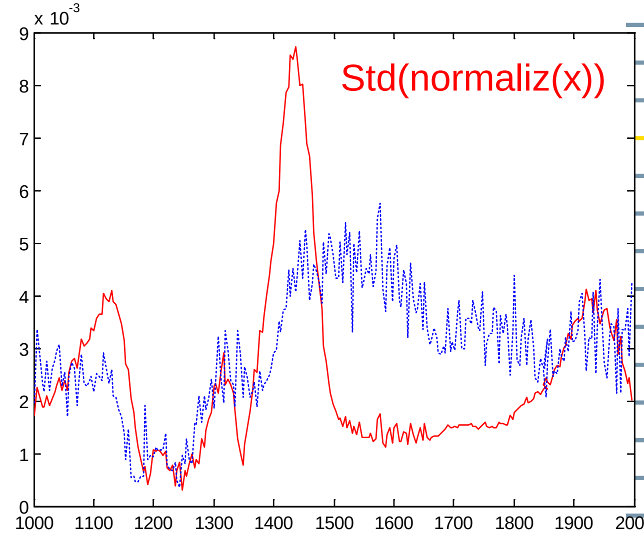
- Flour measurement + GLUCOSE
- 6 channels are measured at the same distance



Raw spectra

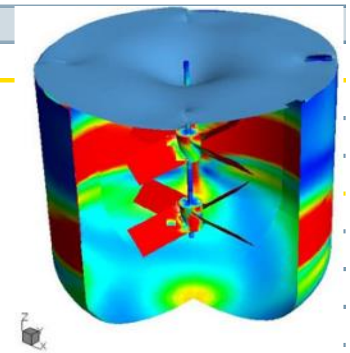


Normalised spectra



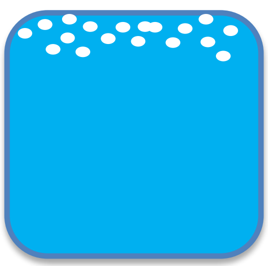
The standard deviation of the positions provides a direct diagnostic of homogeneity

Multiprobe for complex mixing

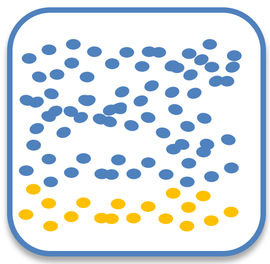


Common problem in mixing

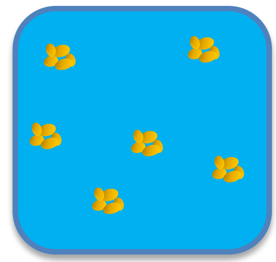
Liquid | Solid | Liquid+solid



creaming

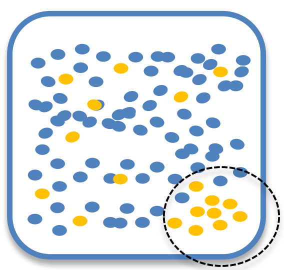


Unmixing / sedimentation

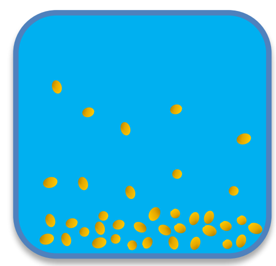


flocculation

Unmixing / coalescence

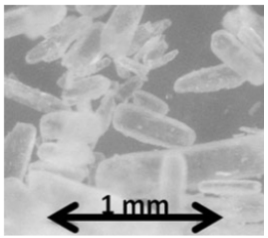


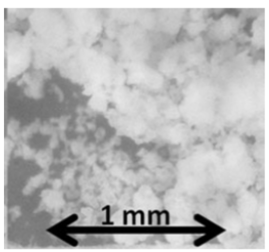
Clog /agglomerates



sedimentation

4. Powder homogeneity





- Blending of Pharmaceutical powders using Multipoint NIR
  - Acetyl Salicylic Acid (rod shape crystals)
  - Lactose mono hydrate Tabletose (spherical particles)

Objective: Process understanding of mixing

- 3 runs with the same composition (50/50) and fill order were performed (pure ASA at the bottom)

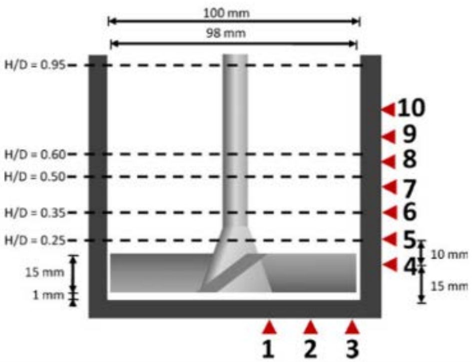
research center pharmaceutical engineering

Scheibelhofer O, Balak N, Wahl PR, Koller DM, Glasser BJ, Khinast JG. Monitoring Blending of Pharmaceutical Powders with Multipoint NIR Spectroscopy. *AAPS PharmSciTech.* 2013;14(1):234-244.

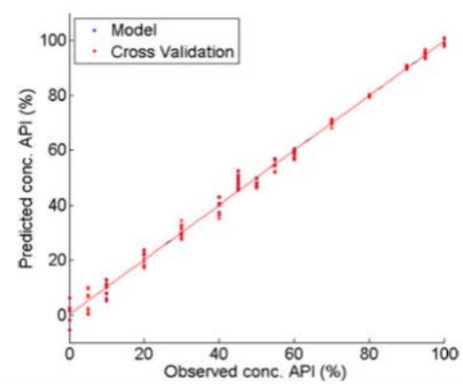
4. Powder homogeneity

CHAUVIN ARNOUX INDATECH

research center pharmaceutical engineering

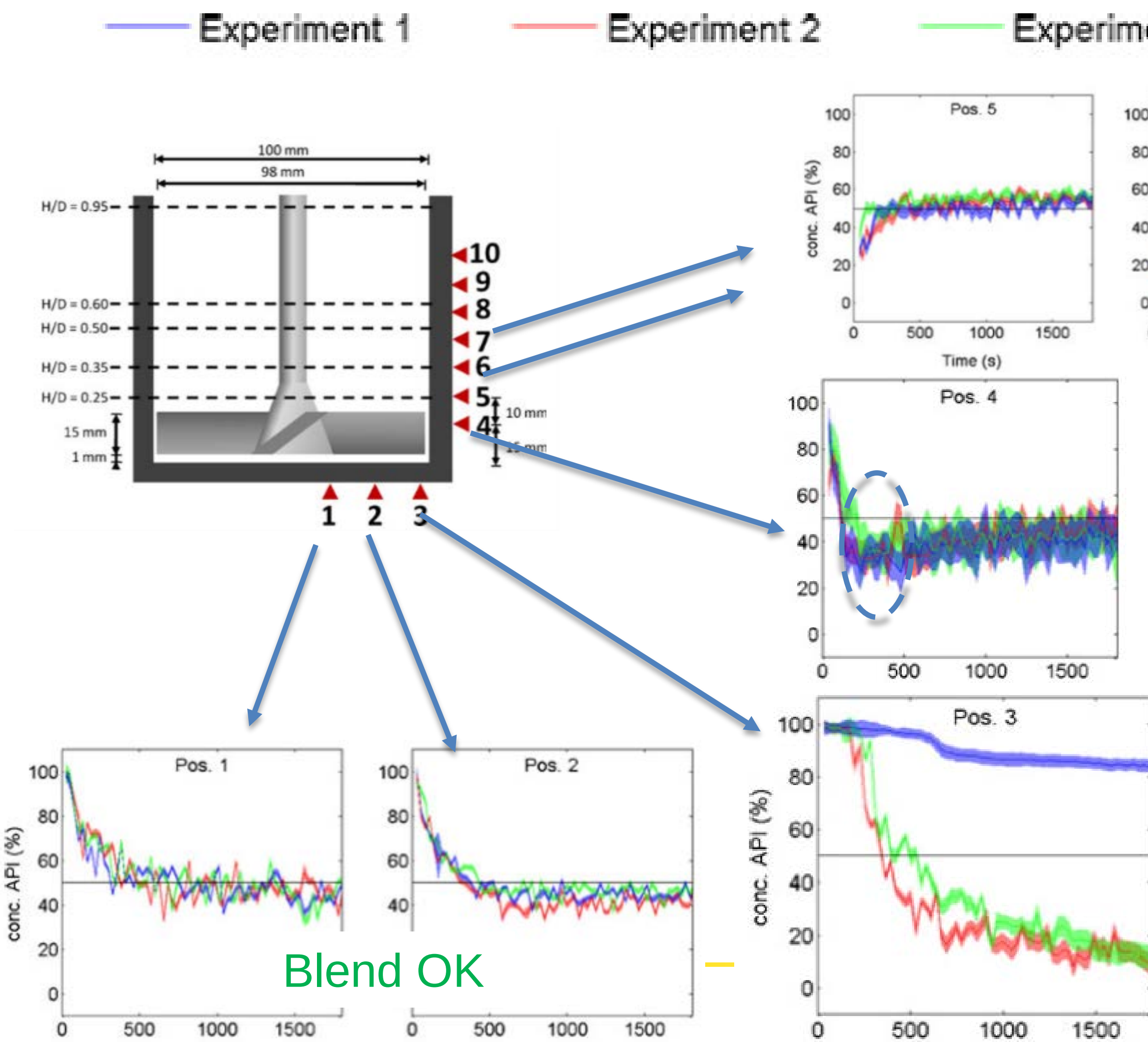


- Setup : 10 optical probes at different depths around the mixer
- Calibration mix :
  [0; 5 10 20 30 40 45 50 55 60 70 80 90 95 100]% API
- SNV preprocessing for API prediction
- Calibration with Unscrambler® X
  - R^2=0.99
  - RMSE=1.5%



Scheibelhofer O, Balak N, Wahl PR, Koller DM, Glasser BJ, Khinast JG. Monitoring Blending of Pharmaceutical Powders with Multipoint NIR Spectroscopy. *AAPS PharmSciTech.* 2013;14(1):234-244.

Determining powder blending dynamics, mixing end-point and homogeneity

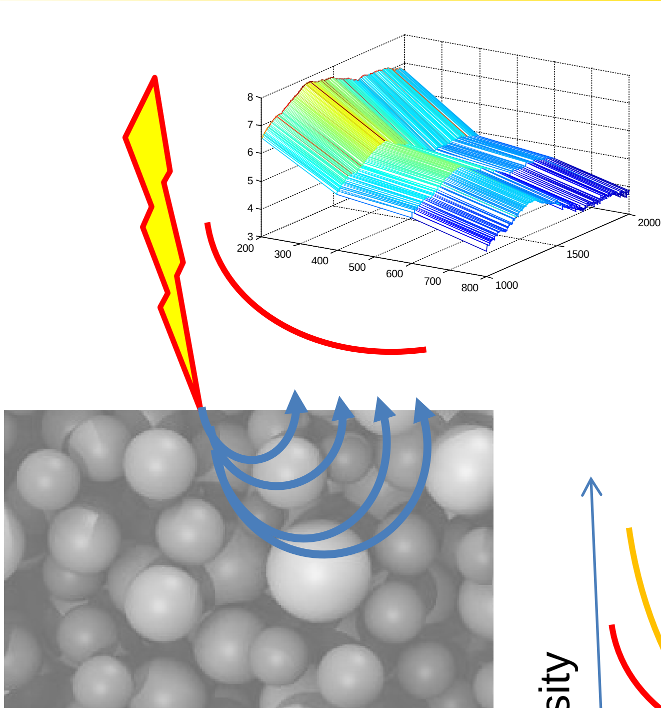


Blend OK

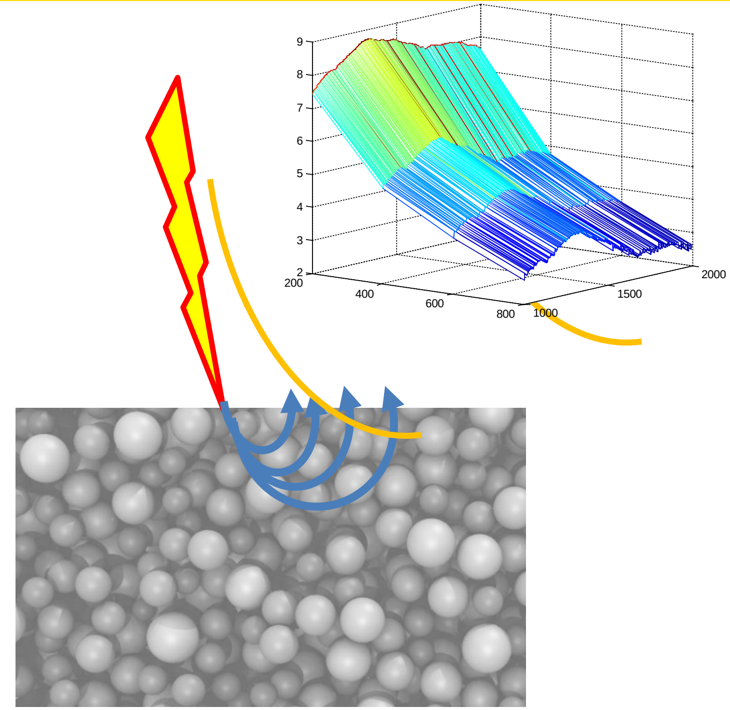
OK but an overshoot appears - over mixed

At the corner of the vessel (position 3), the API concentration is lower
In one experiment the API gets stuck in the corner!

5. Mean Particle Size / Density



Large particles
Lower density



Small particles
Higher density and compaction level

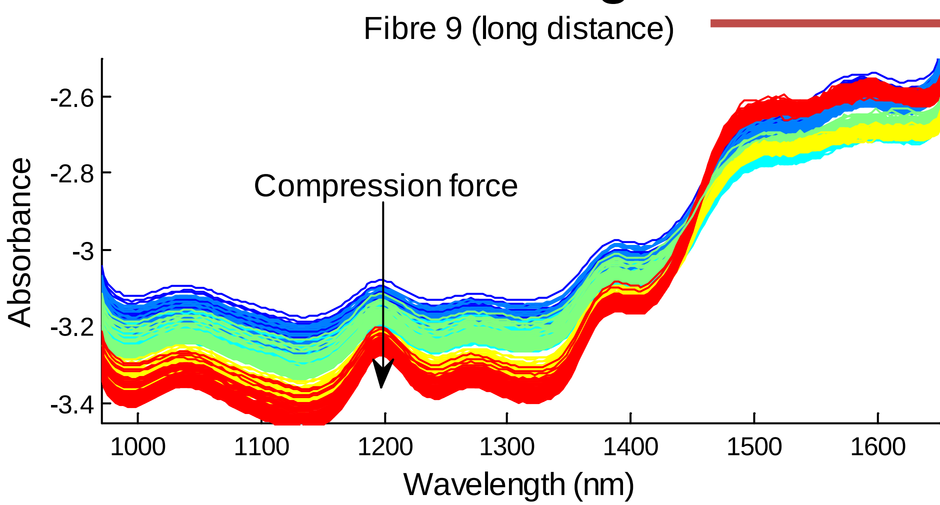
- ➔ Faster decrease of scattering signal with distance
- ➔ Steepest slope

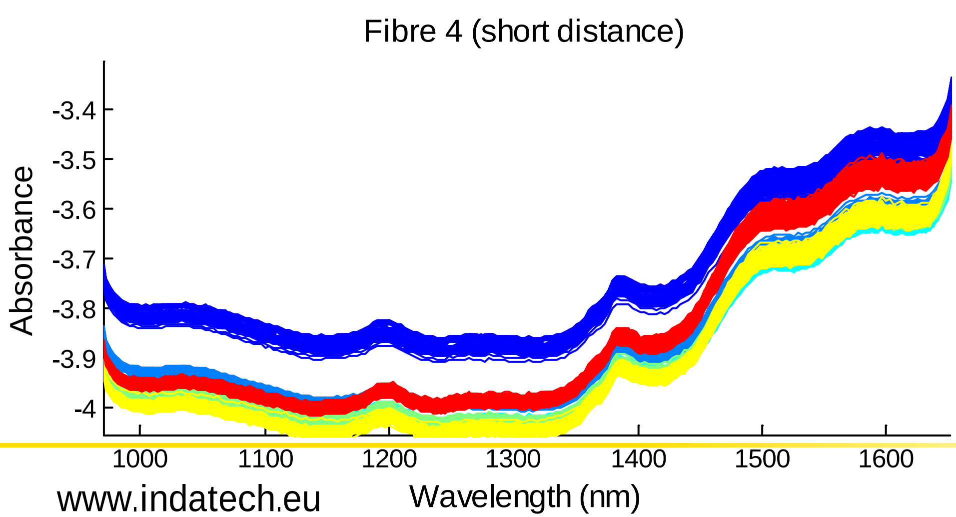
➔ Ratio of 2 extreme positions for density assessment
➔ Standard deviation of several positions

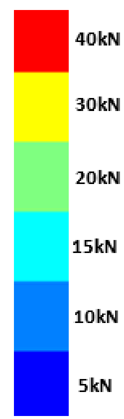
5. Tablet hardness

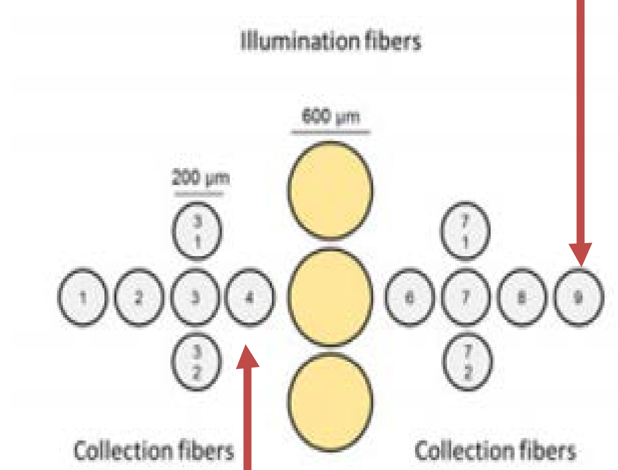
CHAUVIN ARNOUX
INDATECH

Ex: 2 SRS NIR signals and 6 levels of compression force



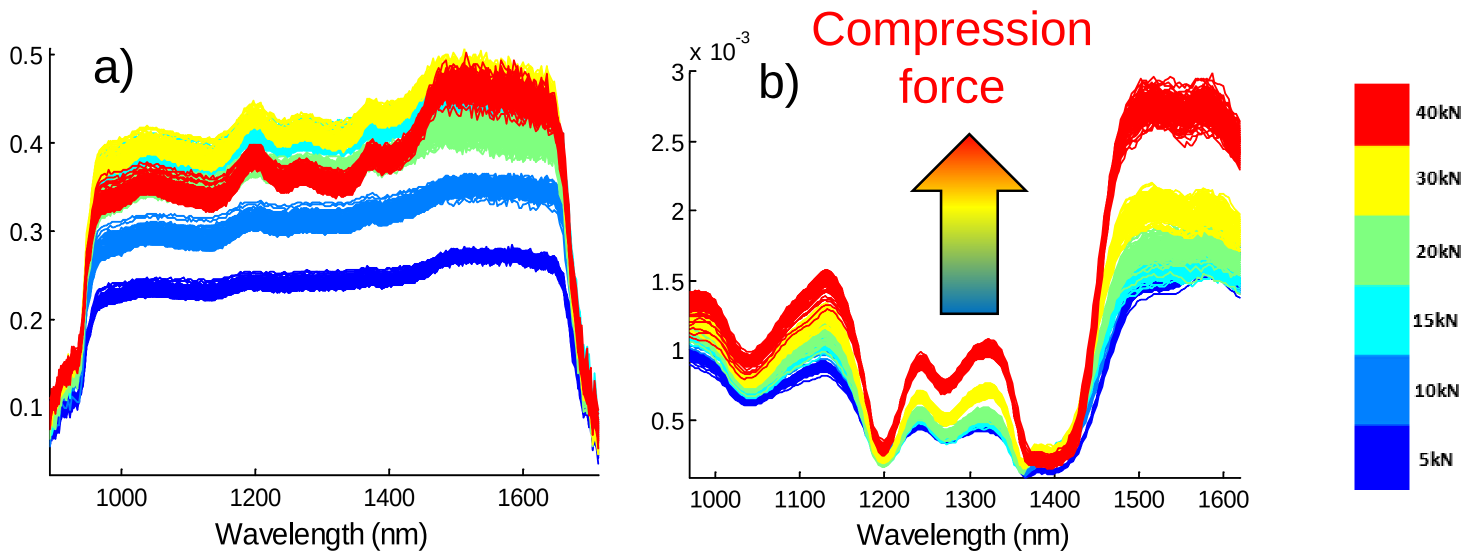






5. Tablet hardness

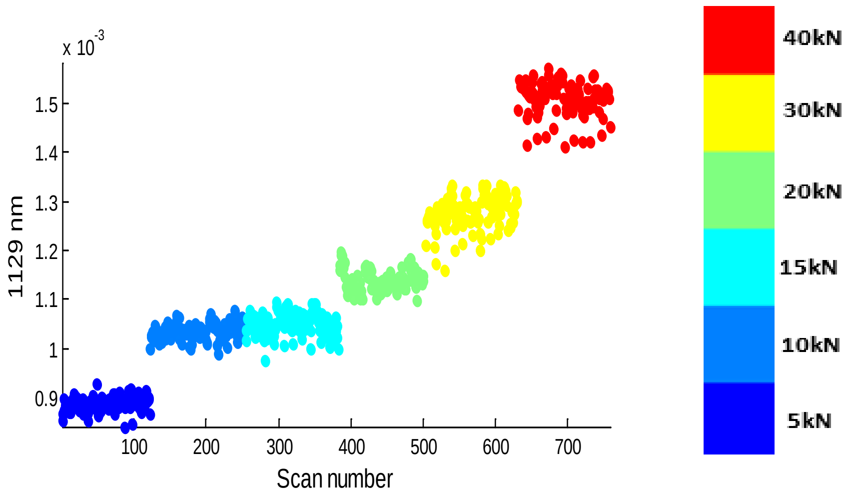
- 8 SRS NIR positions and 6 levels of compression force
  a) Standard deviation spectra of the 8 positions for each compression level
  b) Standard deviation of the normalized spectra of the 8 positions



Standard deviation of the SRS spectra without (a) and with (b) normalization

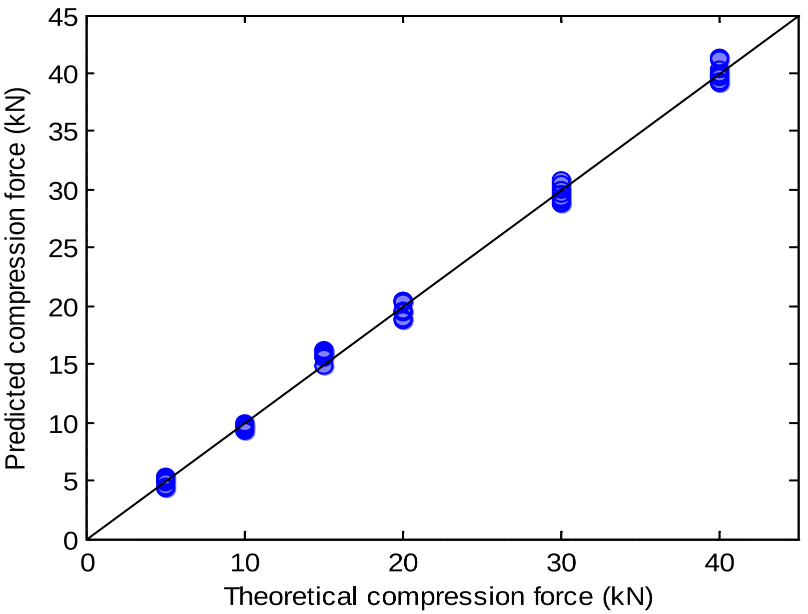
5. Tablet hardness

1) No chemometrics: correlation between the compaction force and the signal at one wavelength



Correlation between compaction force and intensity

2) Chemometrics : PLS model



Presentation outline

- What is Spatially Resolved Spectroscopy (SRS)?
- How to use it?
  - Absorption & Scattering
  - **Chemometrics tools for SAM-Spec® signal analysis**
- In-line SAM-Spec® applications
  - R&D in-line tablet sorting (Servier)
  - High-speed real-time in-line tablet inspection (Proditec)
  - In-line lyo cake inspection (GEA)

R&D inline tablet sorting

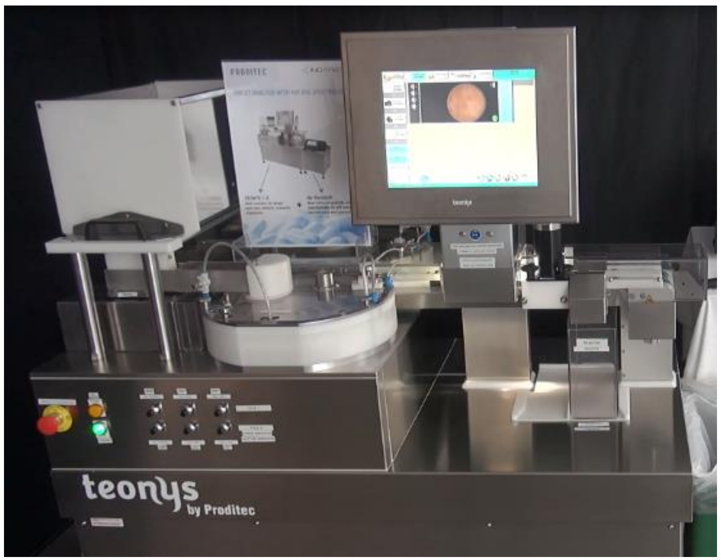
- Set-up:
  - SAM-Spec® probe for tablet composition
  - RGB camera for visual/side inspection
- Predicted parameters:
  - Active Principle Ingredient (API) Content
  - Content Uniformity
  - Tablet Hardness

➔ Servier Laboratory Video

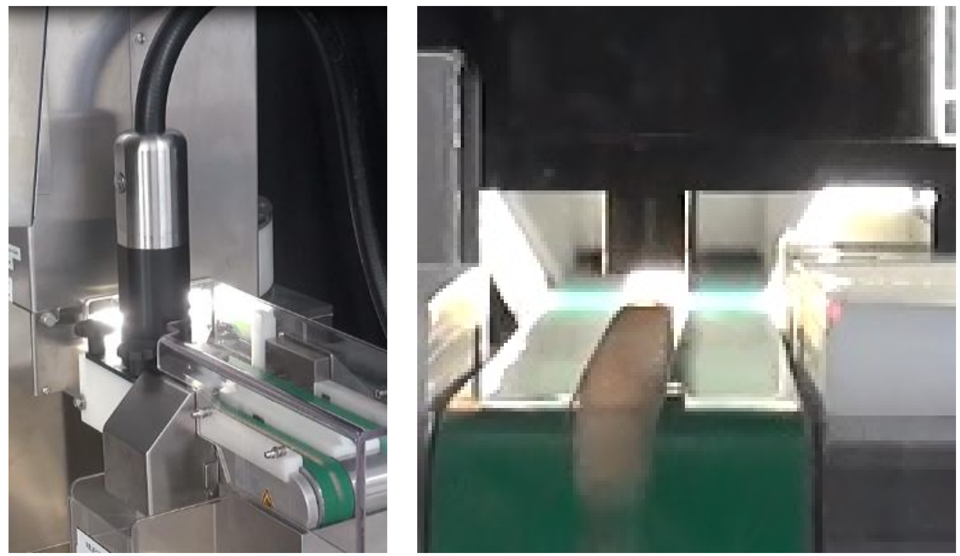
In-line tablet inspection

Teonys inspection machine for tablets and capsules

PRODITEC
AUTOMATIC INSPECTION MACHINES



Visual inspection for defect detection



SAM-Spec® probe for chemical inspection

➔ With double probe configuration : 200,000 tablets per hour

➔ PRODITEC Teonys inspection machine Video

In-line Lyo cake inspection

Biotech products (vaccines, antibodies, etc.) are freeze-dried for storage:
➔ lyophilization cakes in vials

- Moisture Concentration and Cake Density

  SRS : one illumination point and several measurements at different distances.

  - Large distances between measurements provides an assessment of larger sample volumes
  - Measurements at different distances provide physical attributes

- Detection of contaminants such as glass, plastic, metal, melt

  Multipoint imaging approach

  - Use as many measurement points as possible in order to increase the probability of detection

LYOSENSE™ by GEA

CHAUVIN ARNOUX INDATECH

LYOSENSE™ online moisture control sensor unit :

GEA engineering for a better world

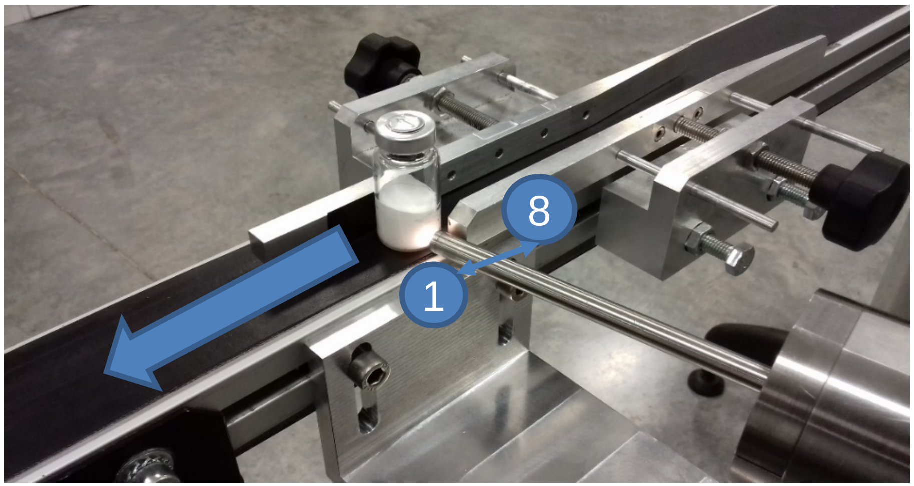
LYOSENSE™ principle

→ Released at ACHEMA, Frankfurt, Germany in June 2018

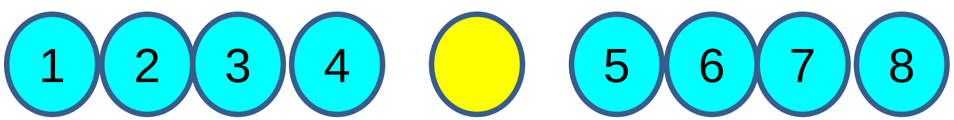
In-line Lyo cake inspection

CHAUVIN ARNOUX INDATECH

Setup for In-line tests (in dynamic)

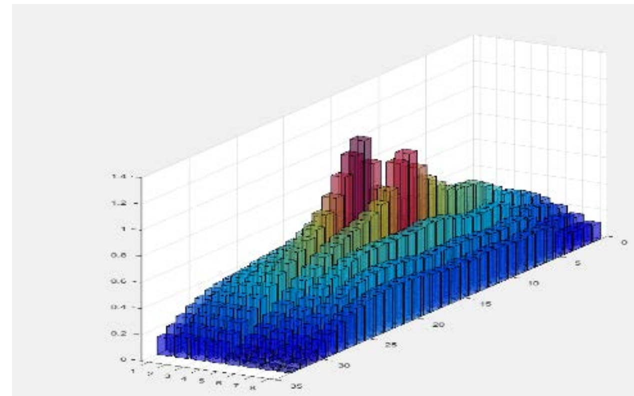


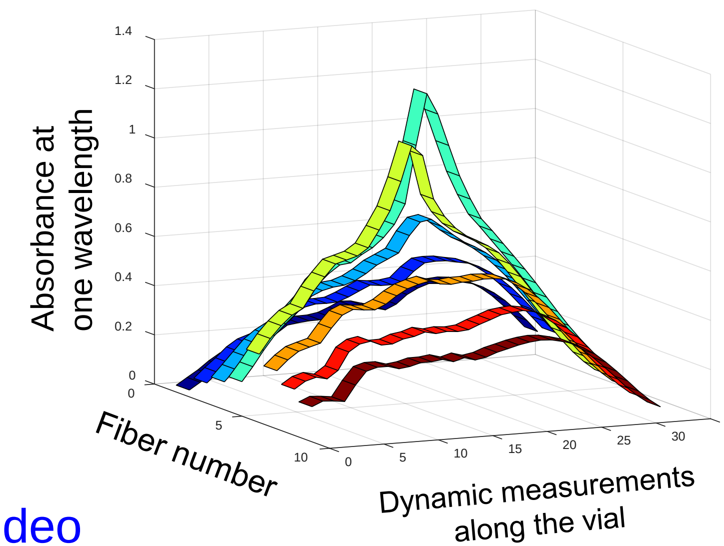
Light source



Fiber number

Fiber number



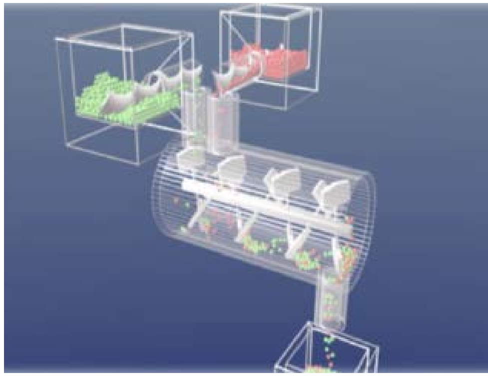


➔ GEA LYOSENSE ™ inspection machine Video

Measure up

Conclusions

- Spatially Resolved Spectroscopy / Multipoint measurement provides key information for critical parameter assessment:
  - Chemical composition
  - Physical parameters
  - Homogeneity / Uniformity
- High-throughput real-time non-contact simultaneous measurements (~ms)
- Multi-probes for critical process attributes:
  - Multilane capabilities to increase inspection speed
  - Multiprobe design for reactor homogeneity
  - Multiprobe design for continuous process (multi-steps)



SPECIAL THANKS

CHAUVIN ARNOUX INDATECH

- INDATECH TEAM
Especially Fabien Chauchard

- Our partners / Co-workers:
  - Servier (France)
  - Proditec (France)
  - GEA (Germany)
  - RCPE (Austria)
  - Montpellier University (France)
  - Duquesne University (USA)

- And all the other partners…

SPECIAL THANKS to the Y2K-compliant Grain Quality Lab - ISU!

CHAUVIN ARNOUX
INDATECH

- Charles R Hurburgh
- Connie Hardy
- Glen Rippke
- Paula Beckman
- Bob Cogdill
- Benoit Igne
- And all the other …

SPECIAL THANKS to the Grain Quality Lab! (PITTCON 1999 in New Orleans)

CHAUVIN ARNOUX INDATECH