SmartSolid Project

In situ monitoring of crystallizations through Spatially Resolved Spectroscopy

PhD director : Denis Mangin – LAGEPP

Supervisors : Emilie Gagnière - LAGEPP
Stéphane Labouret - LAGEPP
Didier Colson - LAGEPP
Noémie Caillol – Axel'One

Romain Kersaudy

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Why monitor crystallizations ?

Crystallization

- Separation and purification process
- Production of crystals with well-defined specifications
- Several complex mechanisms (nucleation, growth, agglomeration)

  → Supervision of both physical and chemical parameters

  → *Ex situ* and *in situ* analysis

In situ monitoring of crystallization

(Non-exhaustive list)

Liquid phase concentration	Solid concentration	Crystal size / Growth	Polymorphism
ATR-FTIR	Raman	FBRM	Raman
ATR-UV/Vis	NIR	PVM	
NIR	Turbidity meter	Imaging / Video probe	
Raman		Acoustic emission	

Objectives

- ➢ Develop methods for *in situ* analysis of physico-chemical parameters of crystallizations with SRS :
  - ➢ Descriptor of particle size distribution
  - ➢ Solid content
  - ➢ Liquid phase concentration
  - ➢ Polymorphism

- ➢ Coupling with *ex situ* and *in situ* analytical methods

Why use the SRS ?

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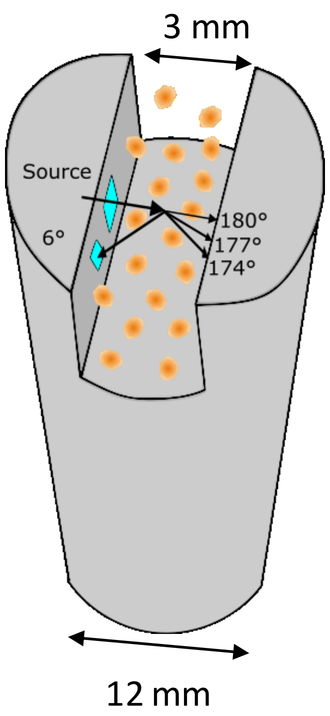
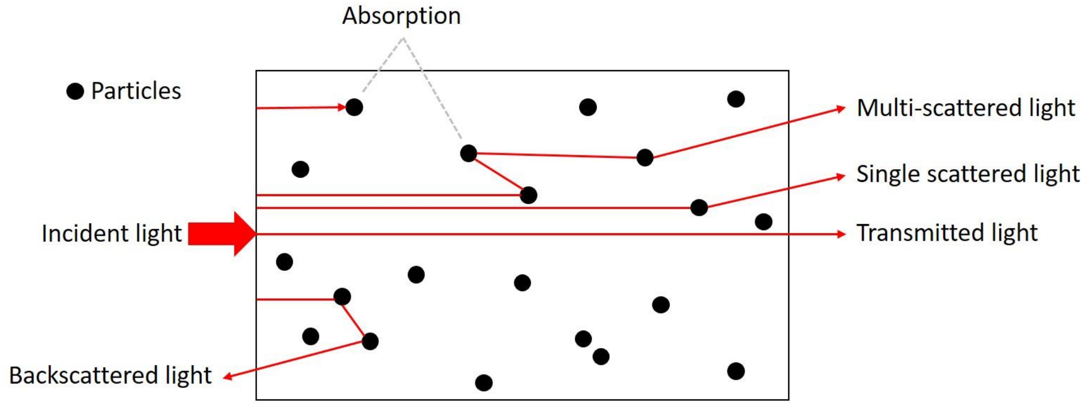
- Light – matter interaction
- Near-infrared detector 900 – 1700 nm
- 4 measurement angles

→ To measure both transmitted and scattered light



Typical crystallization media (suspension)



[1] M. Rey-Bayle et al. Multiangle near infrared spectroscopy associated with common components and specific weights analysis for in line monitoring, JNIRS.(2019)
[2] M. Gheghiani et al. Monitoring of polymer content in an emulsion polymerization using spatially resolved spectroscopy in the near infrared region and Raman spectroscopy, Polym. Eng. Sci. 60 (2020)
[3] M. Gheghiani et al. Online Monitoring of the Particle Size in Semibatch Emulsion Copolymerization Using Spatially Resolved Spectroscopy and Raman Spectroscopy, Ind. Eng. Chem. Res. 60 (2021)

Crystallization set-up

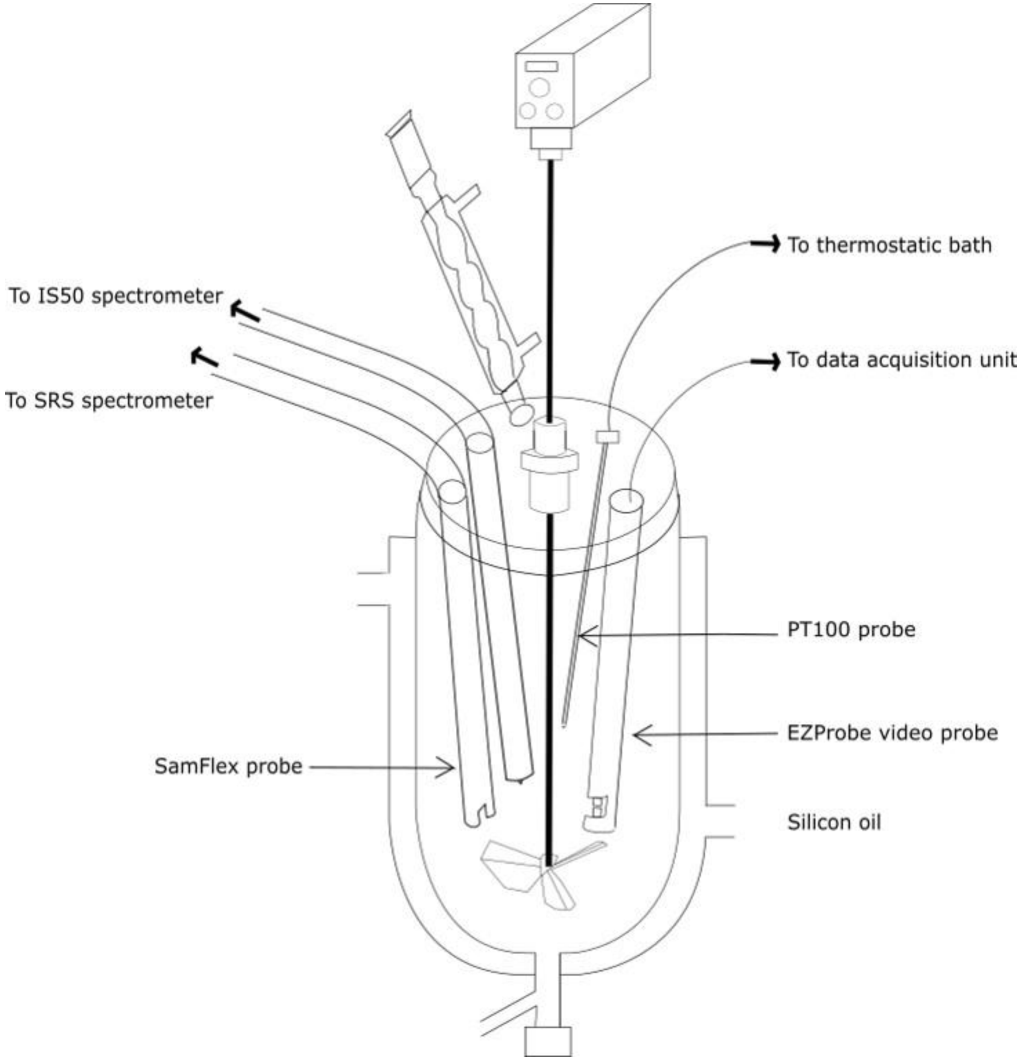
- 2,5L double-jacketed stirred reactor
- Stirrer : Mixel propeller TT type
- Stirring rate : 350 rpm

ATR-FTIR

- Mid-infrared spectroscopy
- In situ ATR probe (5500 – 12500nm)

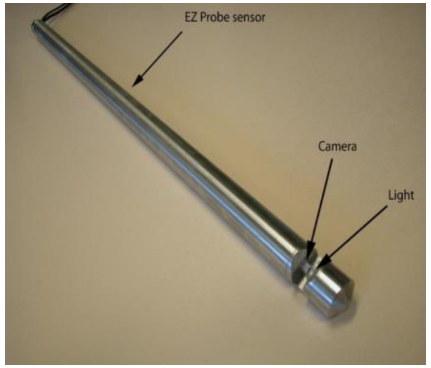
→ Reference method for measuring the liquid phase concentration

SRS Probe



Video probe

→ Used to better understand the SRS spectra variations



Laser granulometry (*ex situ*)

→ Reference method for measuring the particle size distribution

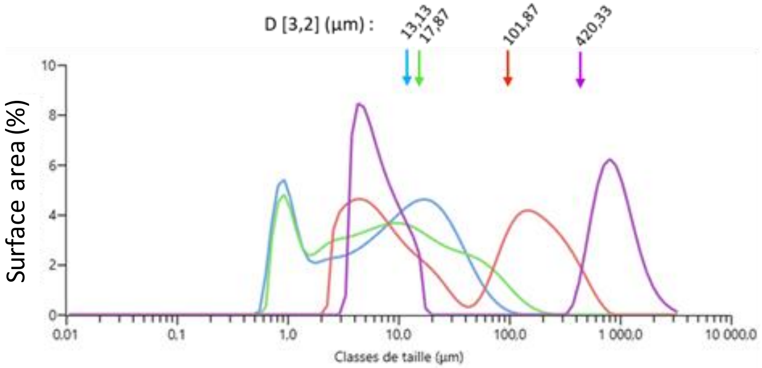
Predictions from calibration database

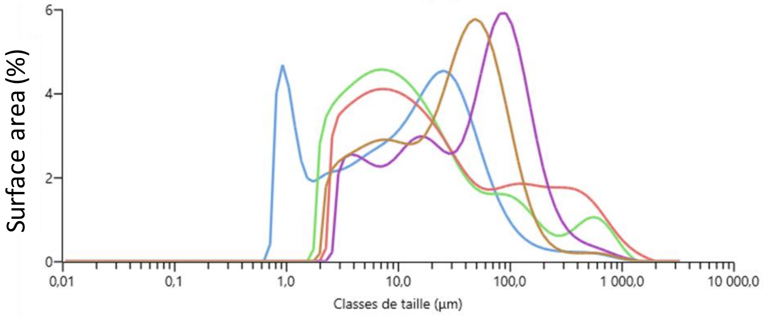
2 organic compounds studied

1st compound (Industrial)

- 4 particle size cuts :
  - 0 – 50 µm
  - 50 – 100 µm
  - 100 – 500 µm
  - > 500 µm

  + mixtures
- 6 solid contents :
  - 1 to 28 w%
- 4 temperatures :
  - 45, 55, 65 and 85°C

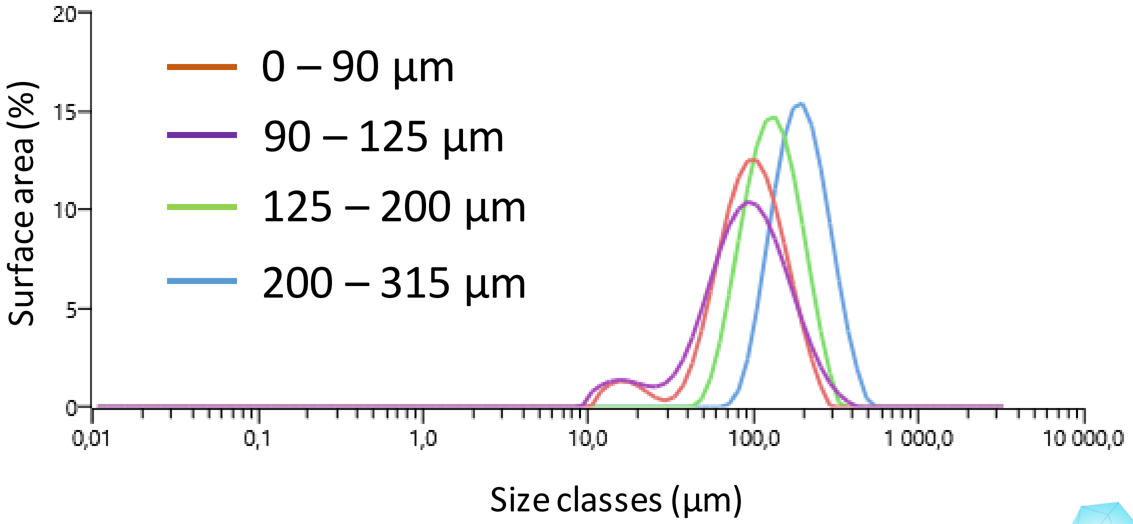




2nd compound (Adipic acid)

- 4 particle size cuts :
  - 0 – 90 µm
  - 90 – 125 µm
  - 125 – 200 µm
  - 200 – 315 µm
- 5 solid contents :
  - 1 to 18 w%
- 1 temperature : 40 °C

Surface particle size distributions



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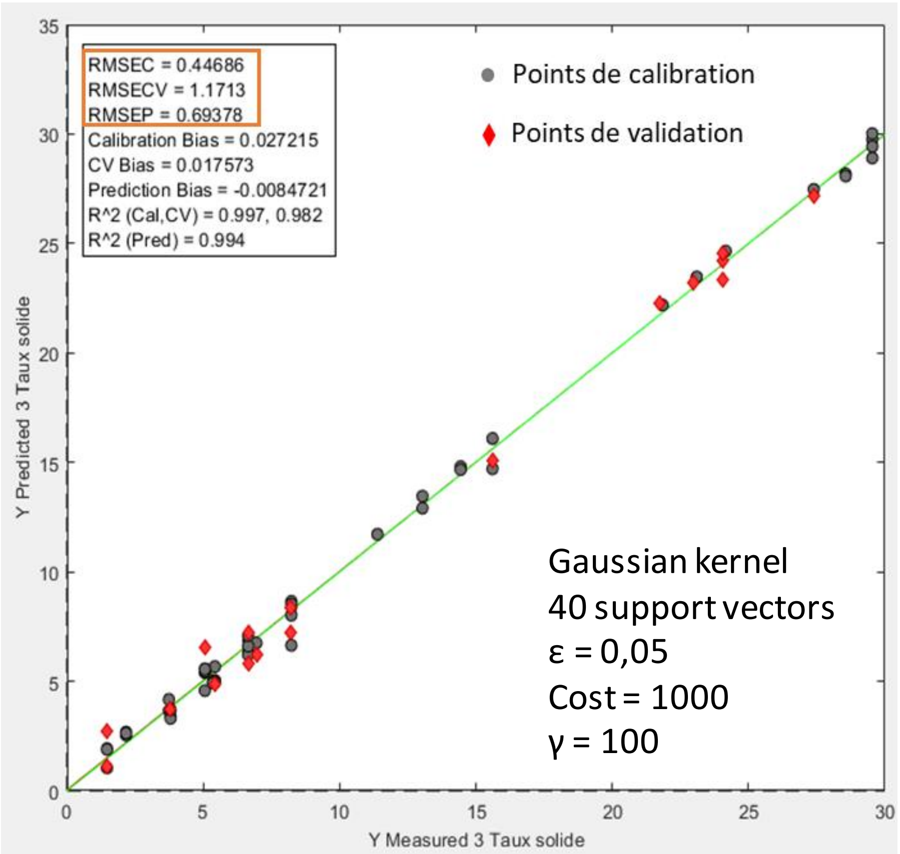
Solid content predictions with Support Vector Machine

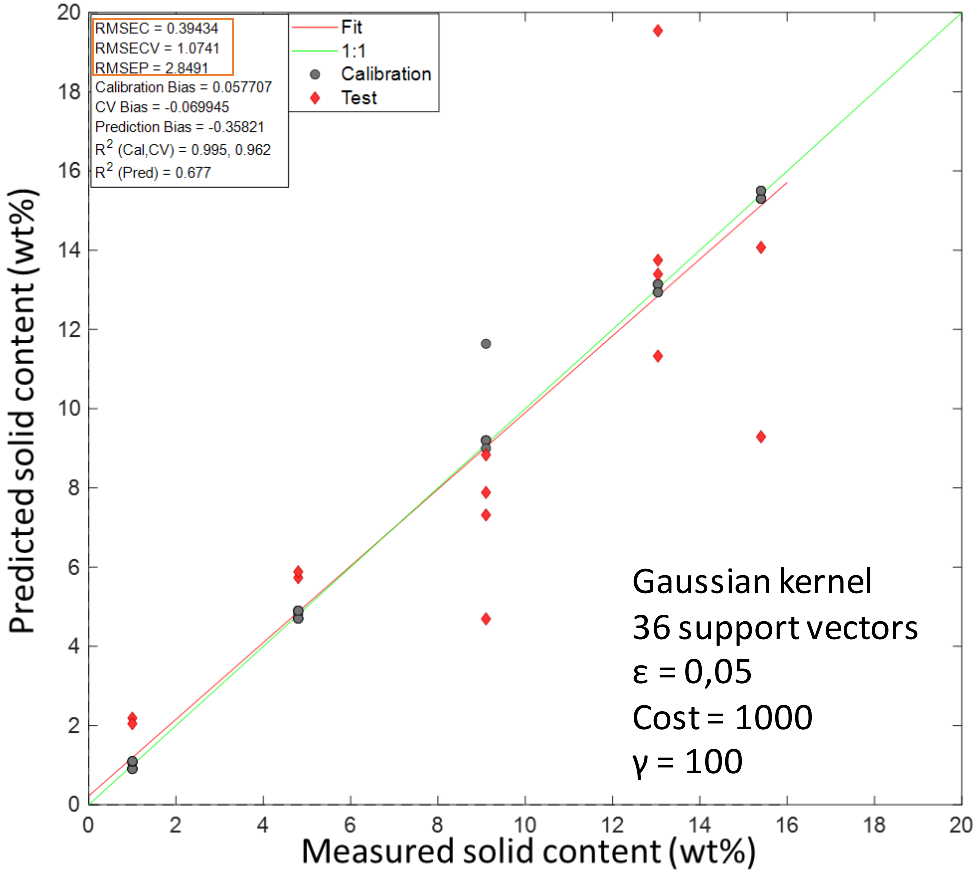
1st compound (Industrial)

- Calibration : 71 spectra
- Test : 23 spectra
- Prétraitements : 1st derivative (pol. Order : 2, window : 15 pts) + normalization



2nd compound (Adipic acid)

- Calibration : 42 spectra
- Test : 16 spectra
- Prétraitements : 1st derivative (pol. Order : 2, window : 15 pts) + normalization

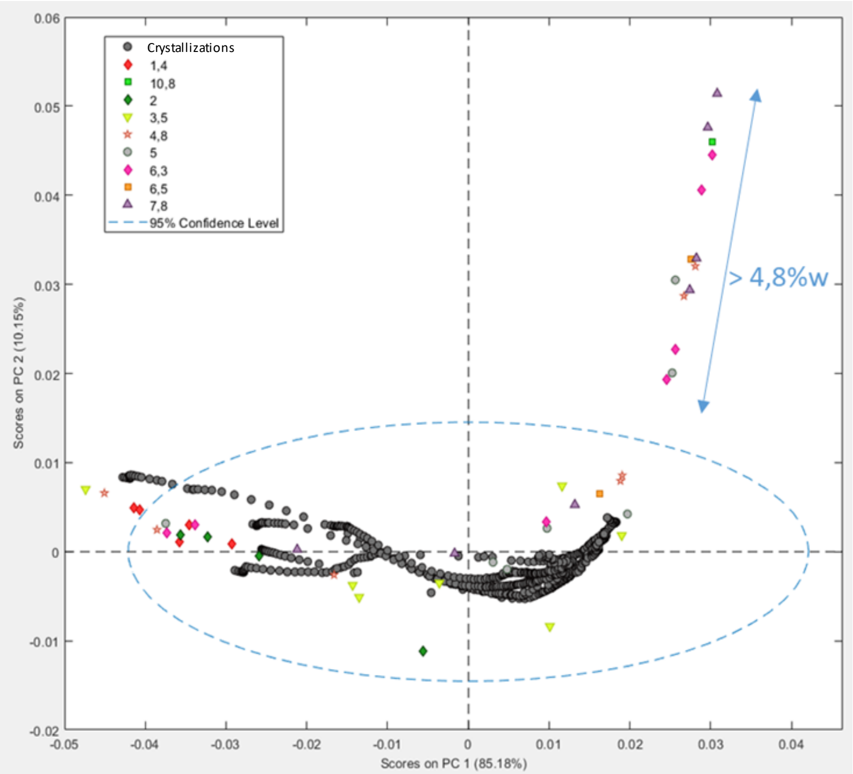


Predictions from calibration database

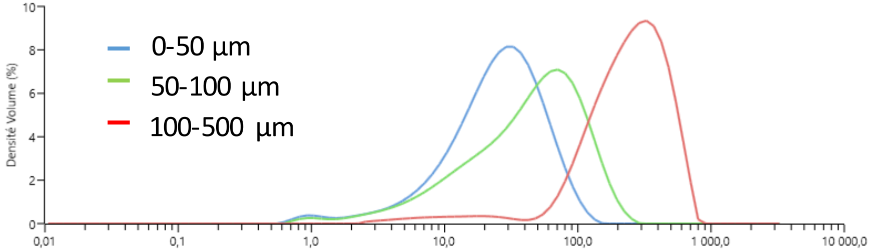
Solid content predictions with Support Vector Machine

→ Impossible to use the model to predict solid content during crystallizations

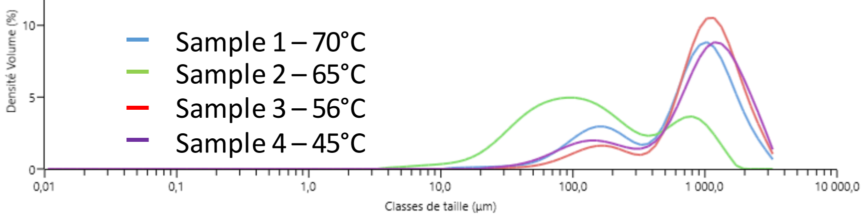
- Different reasons :
  - Crystal habits
  - Surface properties
  - Particle sizes



Size distribution - calibration

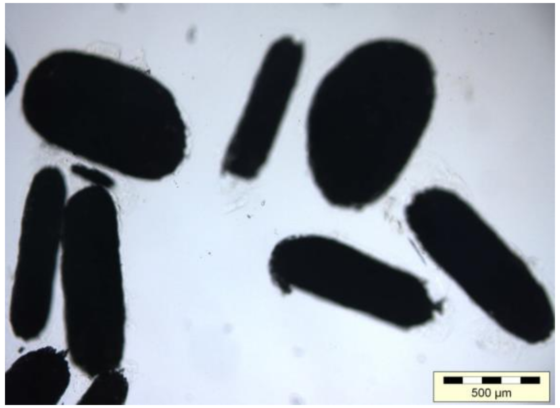


Size distribution - crystallization

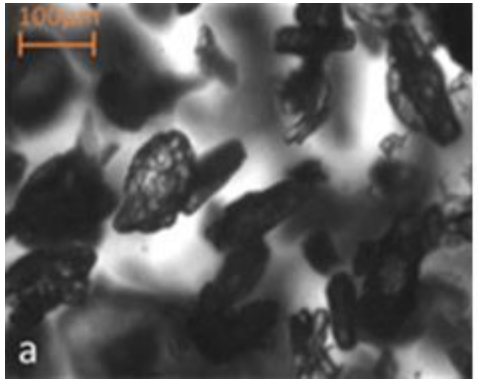


Microscope images – calibration powder

Crystals in suspension after a long period of stirring



Images from video probe- crystallization



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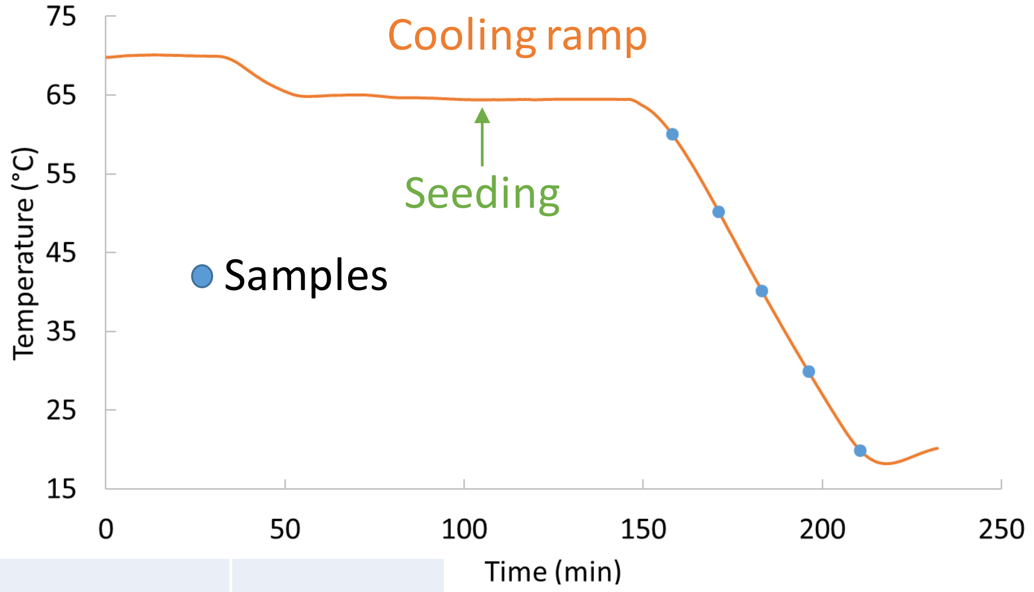
Crystallization experiments

- Batch Cooling crystallizations
- From 70°C to 20°C (-1°C/min) with temperature step at 64,5°C to seed
- Varying initial concentration, seeding method and seed mass



Batch	Starting solution	Initial concentration (wt%)	Seeding	Wet / dry seed	Seed mass (g)
1	new	20,0	non	-	-
2	new	20,0	non	-	-
3	new	20,0	non	-	-
4	batch 3	21,23	unintentional	-	-
5	new	19,67	oui	wet	5,6
6	new	20,25	oui	wet	5,6
7	new	19,99	oui	dry	5,2
8	batch 7	19,94	oui	dry	5,2
9	new	19,89	oui	dry	5,2
10	batch 9	20,17	unintentional	-	-
11	new	19,87	oui	dry	2,6

Fouling of the SRS probe

Calibration set

Test set

Predictions from crystallization data – Solid content

PLS model

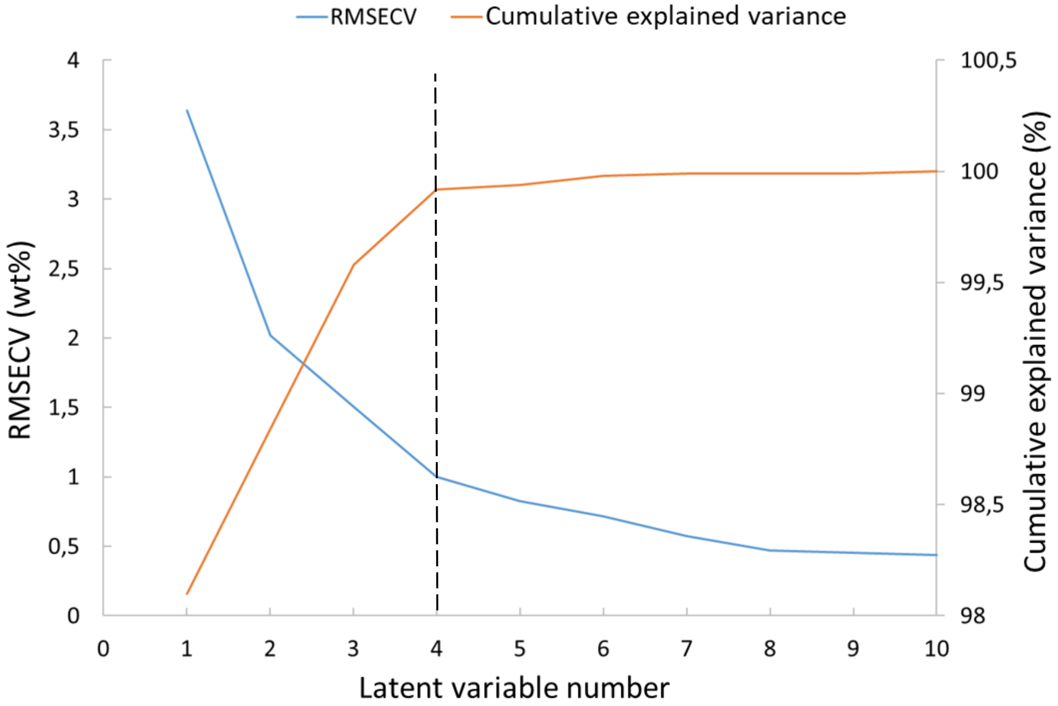
Preprocessing : Savistky-Golay smoothing (window : 5 pts)
Area normalization
Mean centering

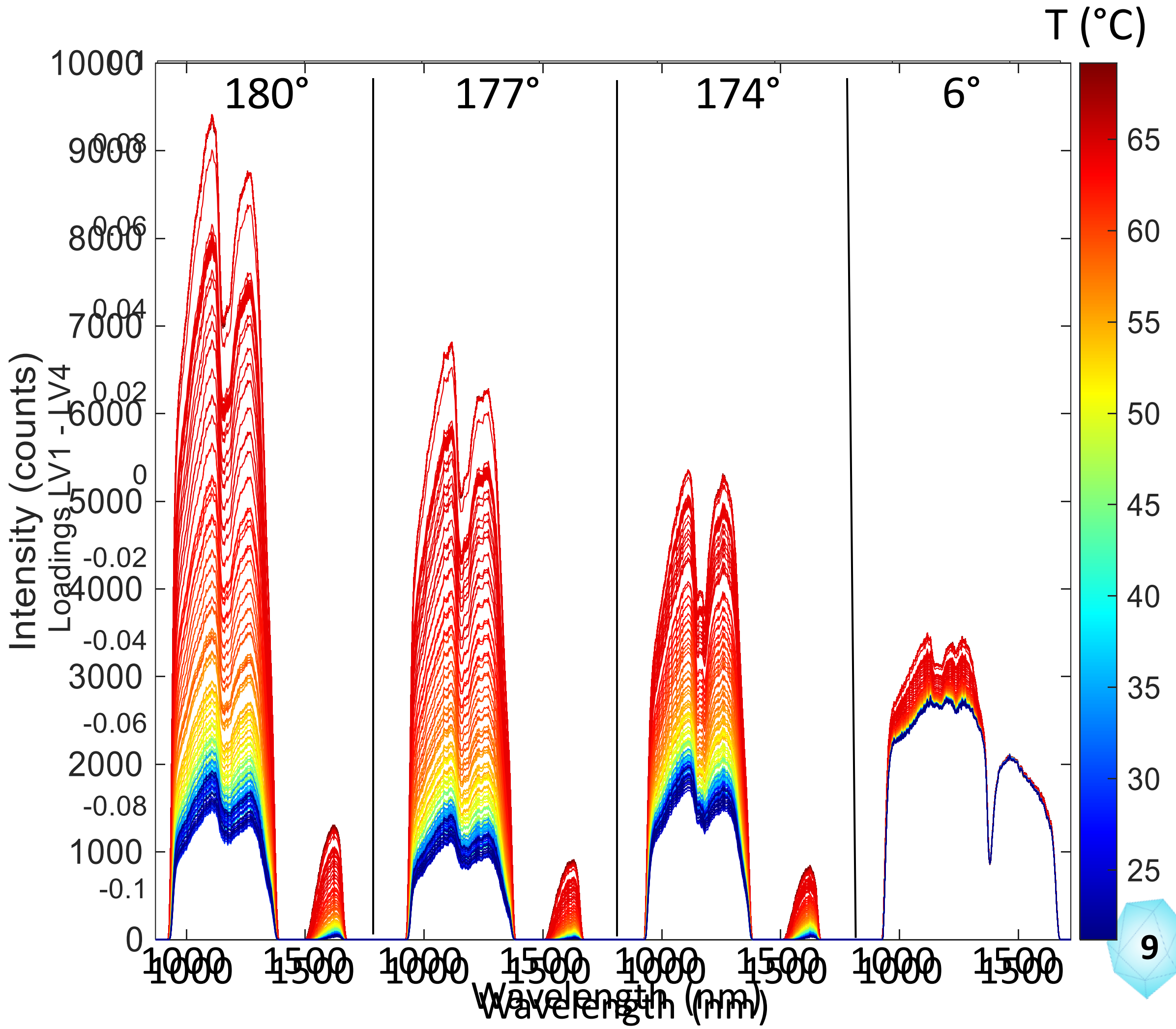
X values:

- SRS spectra acquired during crystallizations

Y values for solid content :

- Measures from samples not representative
- Theoretical values calculated from solubility curve and initial concentration measured

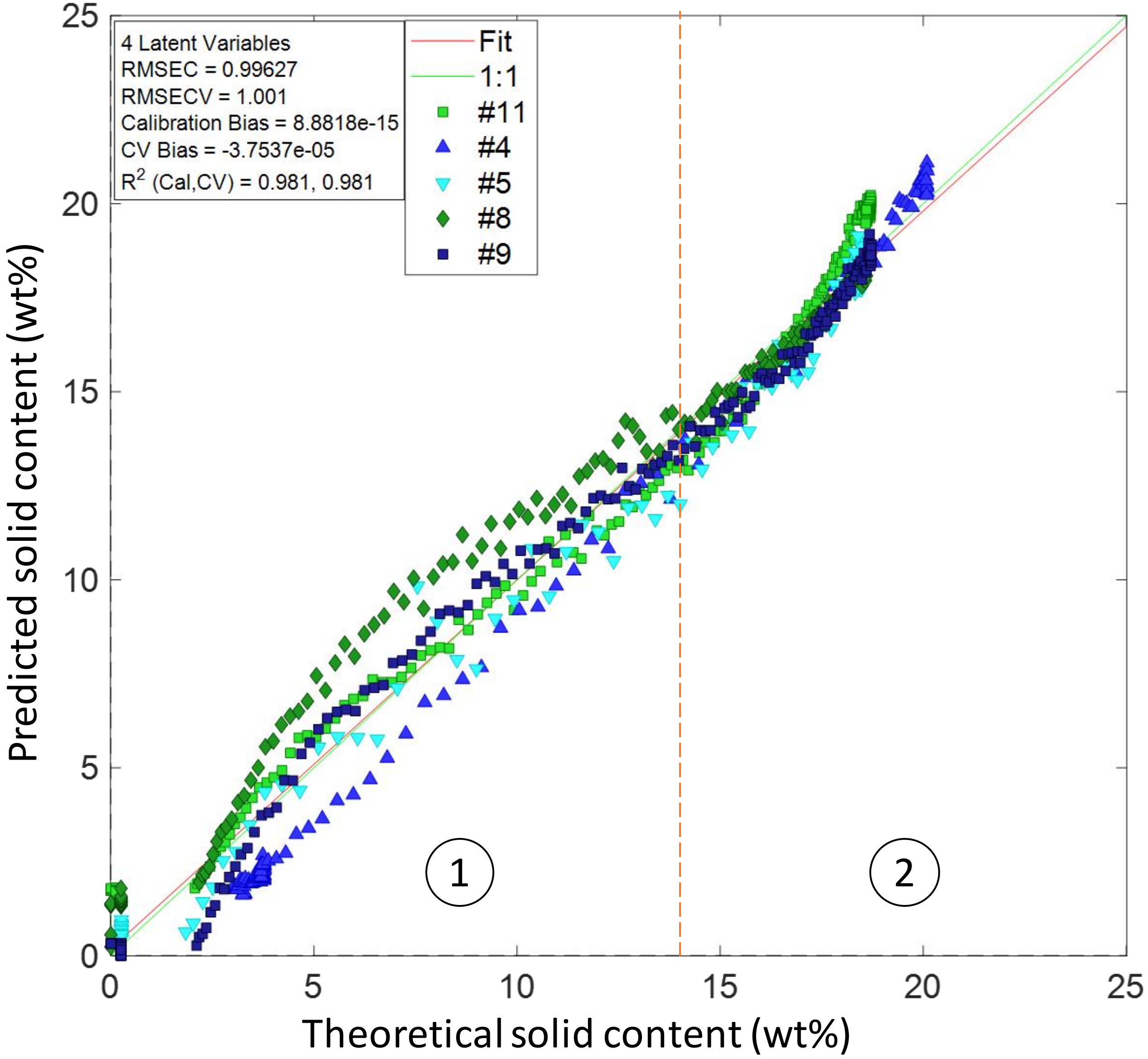




Predictions from crystallization data – Solid content

PLS model

Calibration set predictions



2 stages :

1 1^{st} part of crystallization

- Strong evolution of the number of particles
- Fast crystal growth

Important inter-batch variability caused by seeding variations

→ Important spectral variability causing prediction errors

2 2^{nd} part of crystallization

- Slow increase of solid content
- Very slow crystal growth

Small inter-batch variability – crystals formed tend to the same crystal habit and close sizes

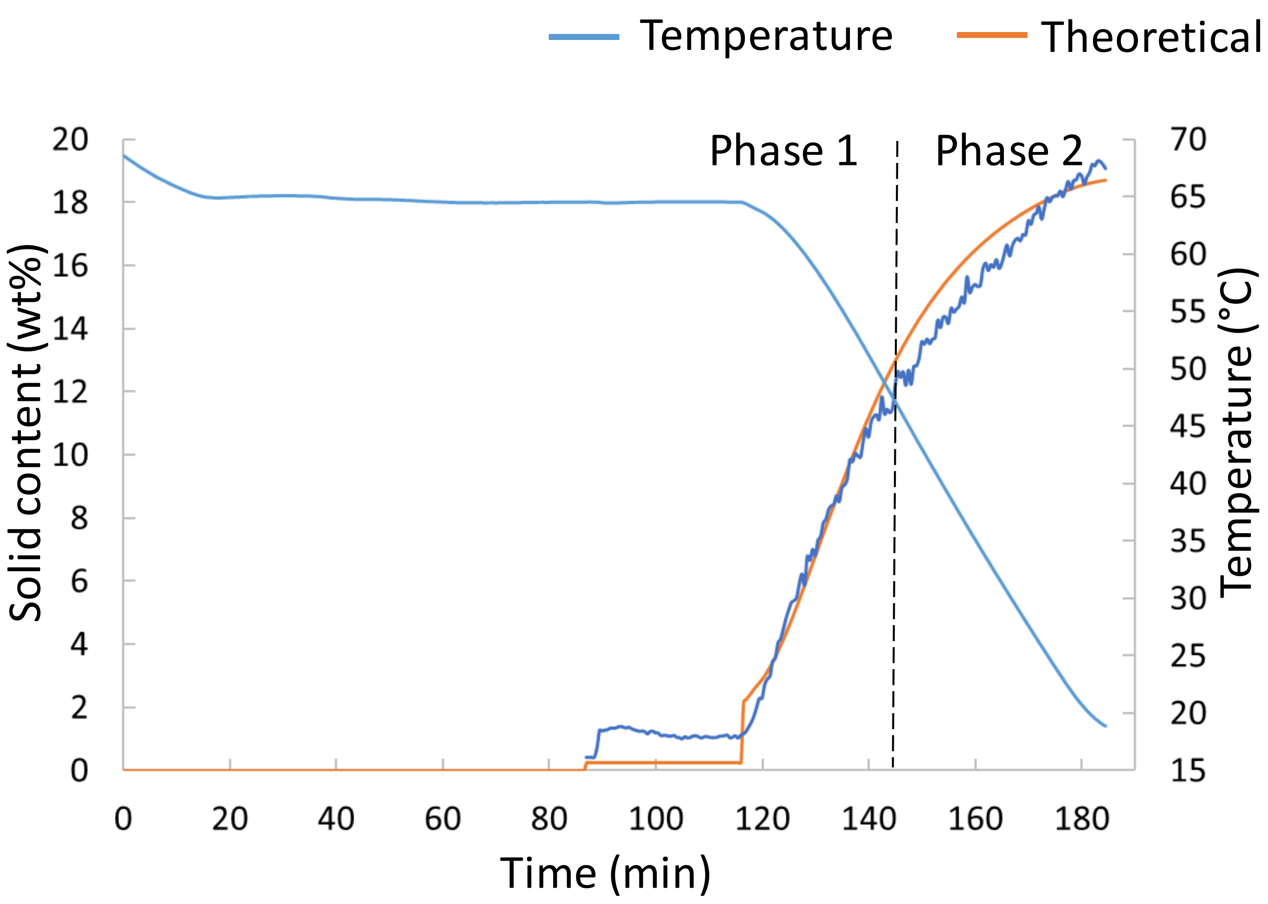
→ Small inter-batch spectral variability causing good predictions

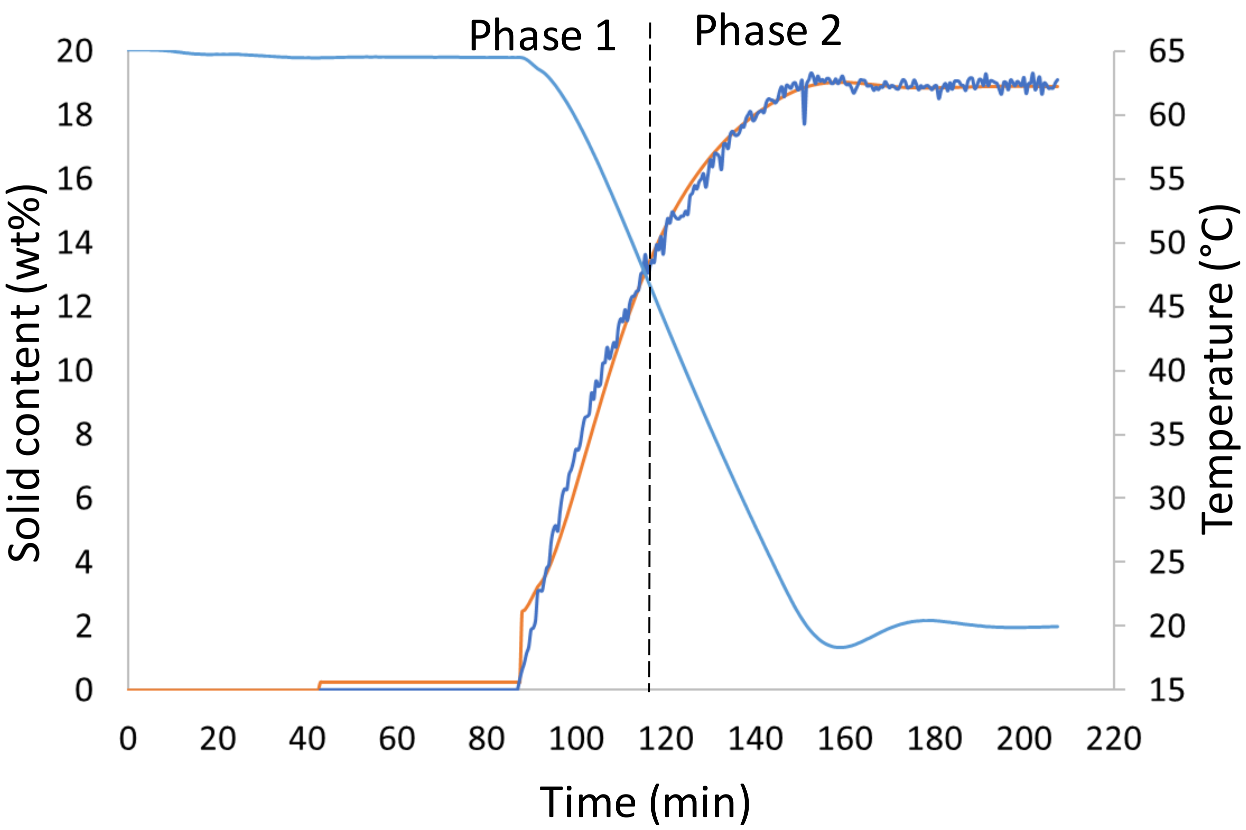
Predictions from crystallization data – Solid content

Test set predictions

Batch #7 – Dry seeded crystallization

Batch #10 – Unintentionally seeded crystallization





Errors at the beginning during seed stabilization

→ Due to very small solid content values not included in the model

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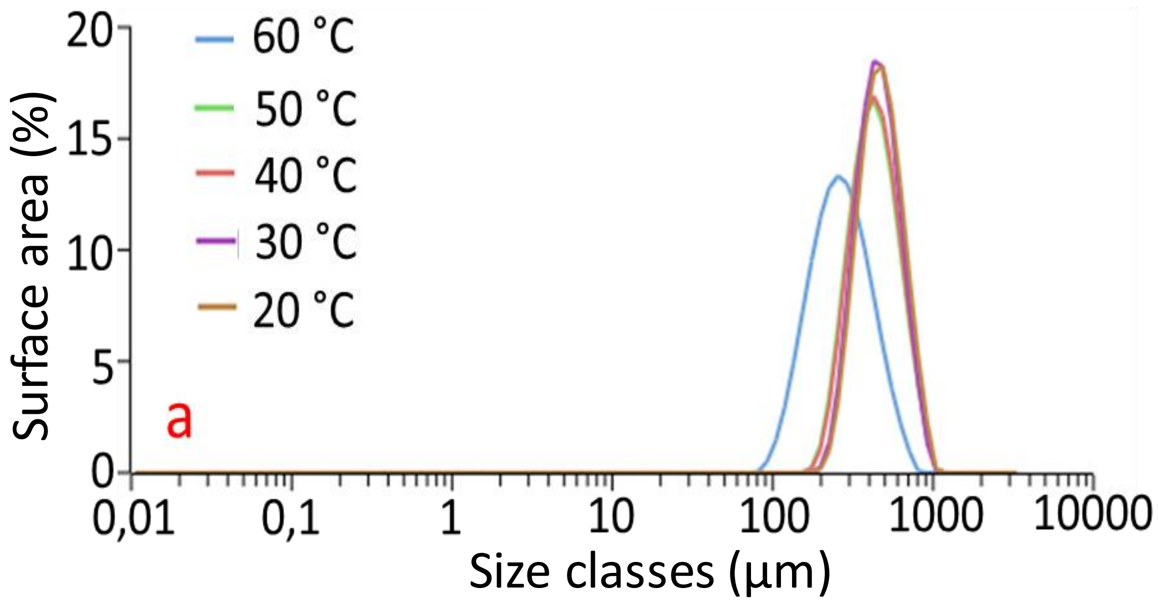
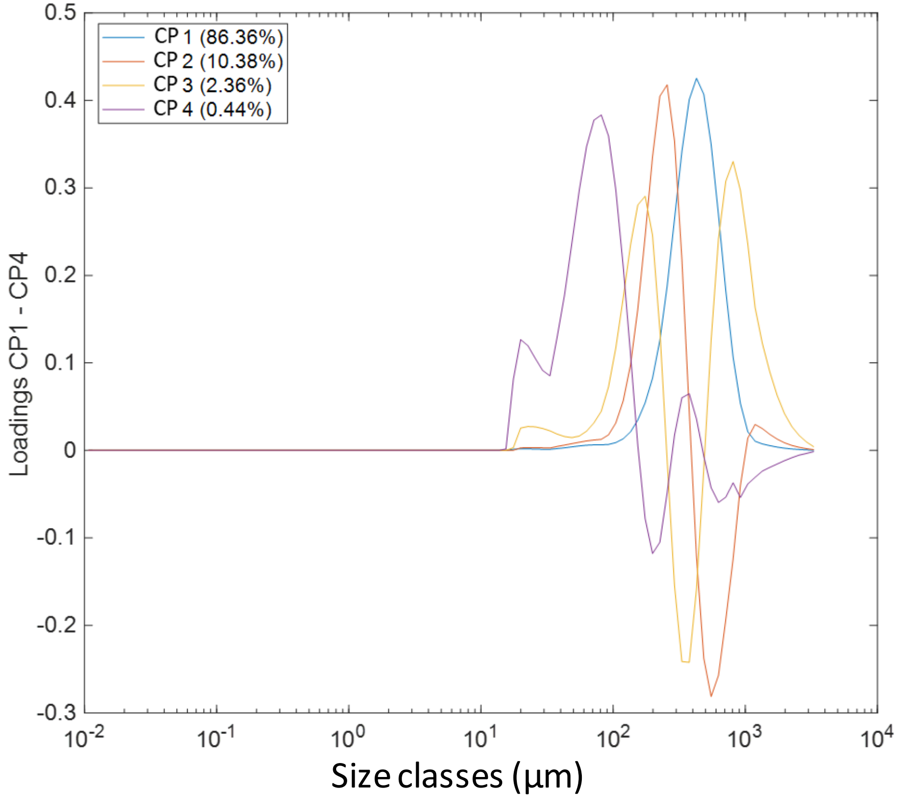
Particle size distribution descriptor choice

- No model was found to predict classical descriptors
- Other approach imagined :
  - → Represent crystal size distributions of the samples by principal components calculated by PCA
  - → Predict the scores on each principal component





4 components needed :

- PC1 and PC2 explain the population between 100 and 1000 µm
- Part of PC3 explain population above 1000 µm
- PC4 explain population of fines between 10 and 100 µm

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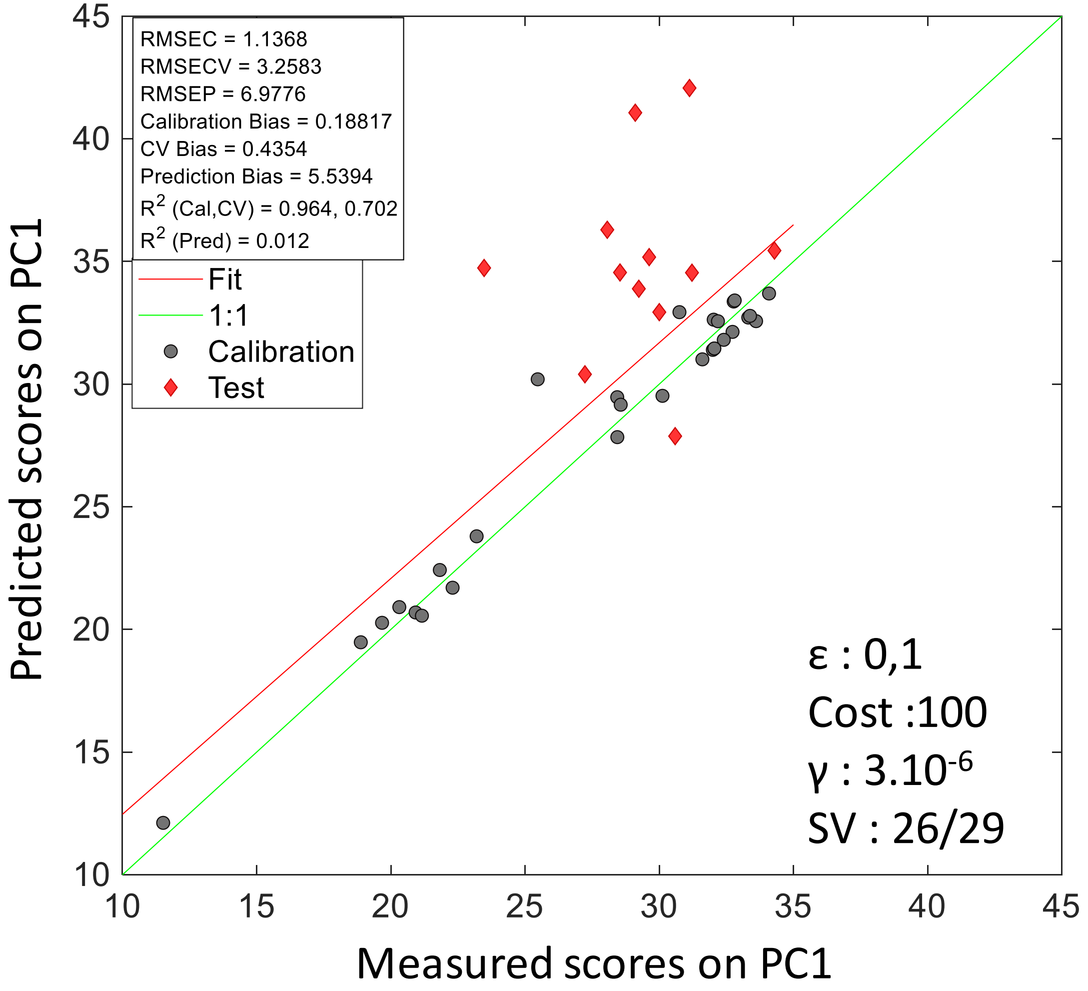
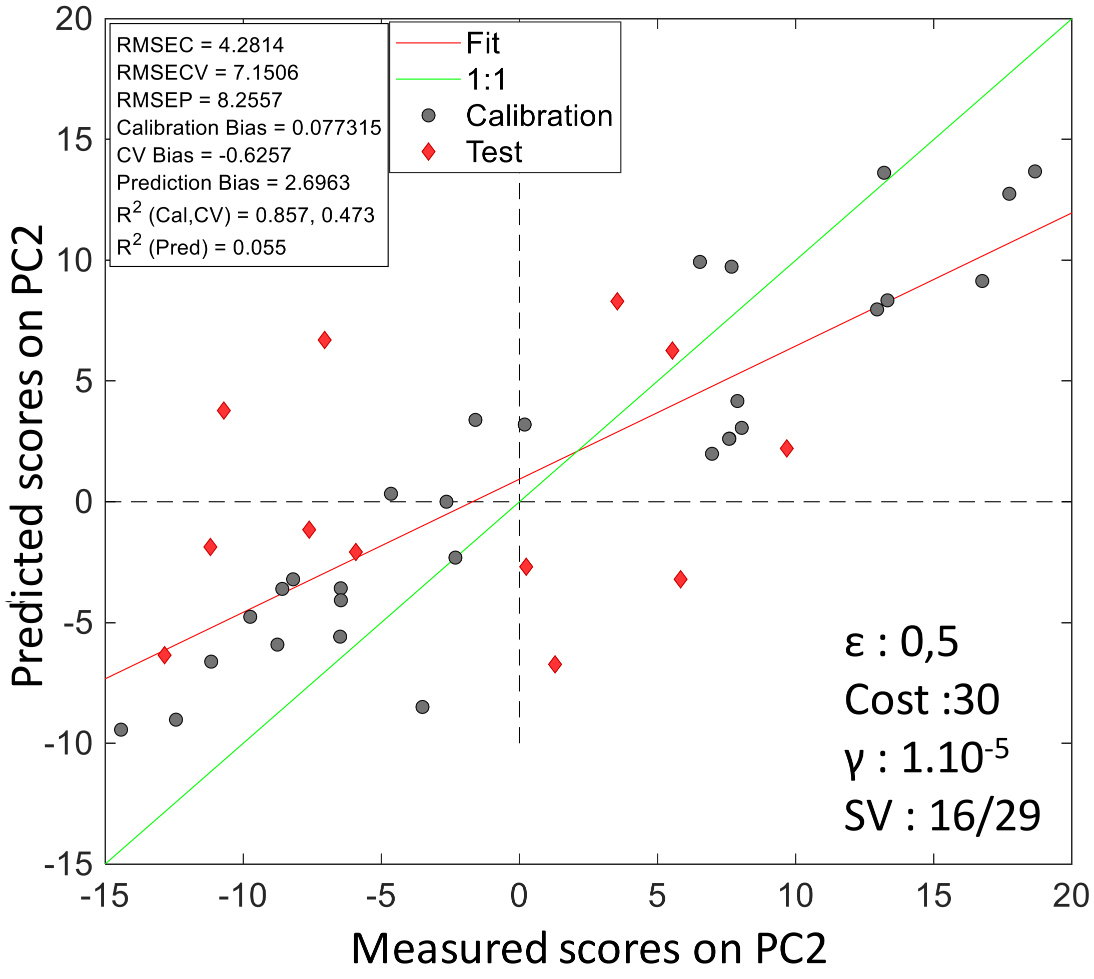
Prediction Models

Prediction of PC1 and PC2 with SVM-R models

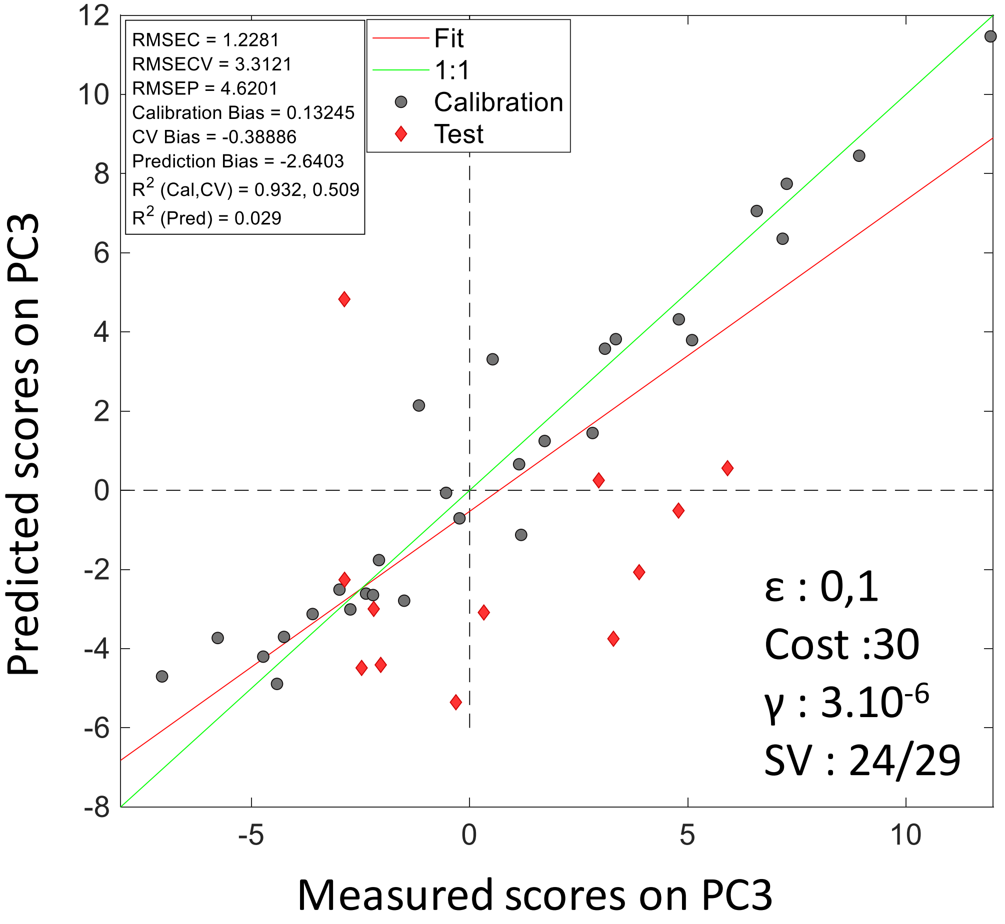


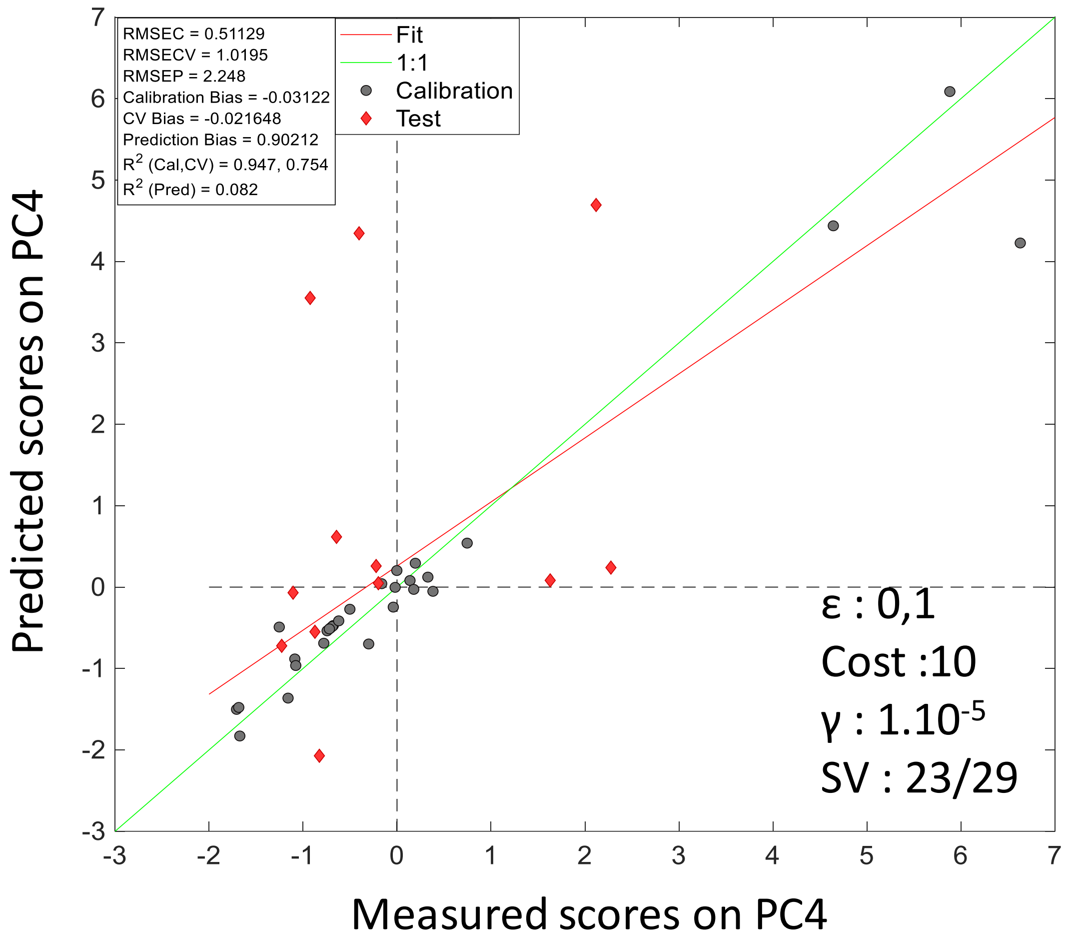


Predictions from crystallization data and samples – Crystal size

Prediction Models

Prediction of PC3 and PC4 scores with SVM-R models





- Easier to find a relationship between the spectra and these descriptors
- Not enough data to build a robust model taking into account a large number a various PSD

Conclusions - Perspectives

Conclusions :

- It is very difficult to build relevant models of physical parameters as solid content and crystal size from synthetic calibration samples
- It is a lot more accurate from data acquired during crystallizations
- SRS associated with PLS model allows the prediction of solid content during adipic acid cooling crystallization
- It is hard to find a good descriptor of PSD because of multimodal distributions
- Prediction of PCA scores of the PSD seems to be a promising approach, but it requires a large database

→ We have reached the limits of the probe in term of sizes

Perspective :

- Expanding the database could allow the use of more advanced algorithms (basic ANN, Deep learning method) to model the strong non-linearities caused by the complexity of light scattering

LAGEPP

Université Claude Bernard Lyon 1

Axel'One

romain.kersaudy1@gmail.com

Hélio SPIR

LinkedIn

Romain Kersaudy
PhD Student - LAGEPP - Université Claude Bernard Lyon 1

Thank you for your attention

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