CMAC
FUTURE MANUFACTURING RESEARCH HUB

Application of Nanofocused X-ray tomography and Image Processing for the Quantitative Analysis of Pharmaceutical Particulate Solid Products

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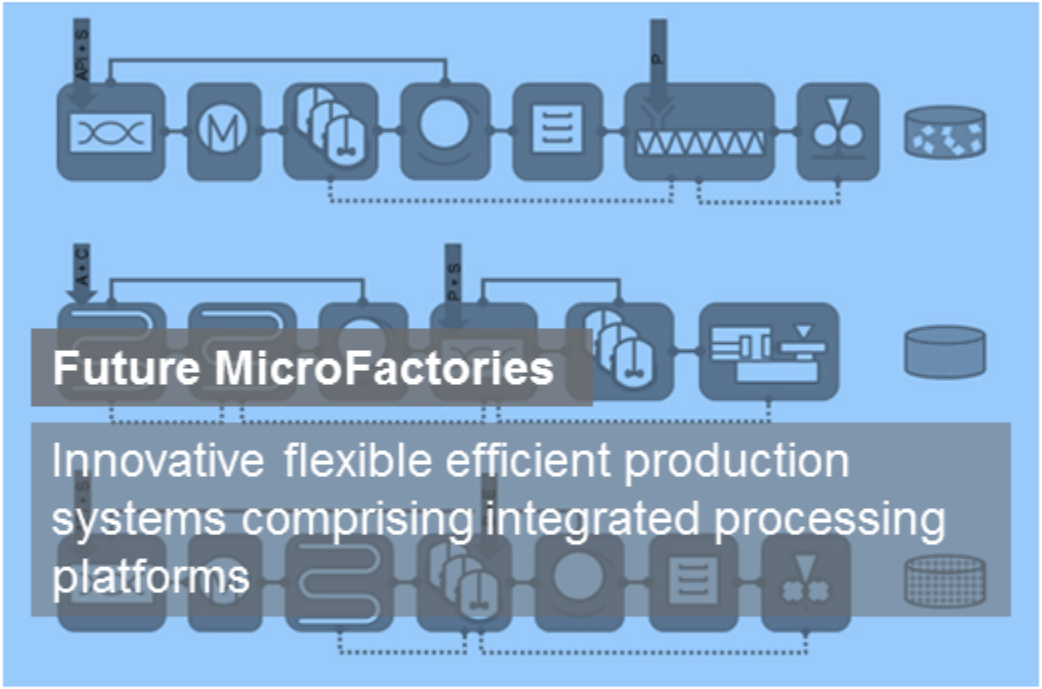
University of Strathclyde

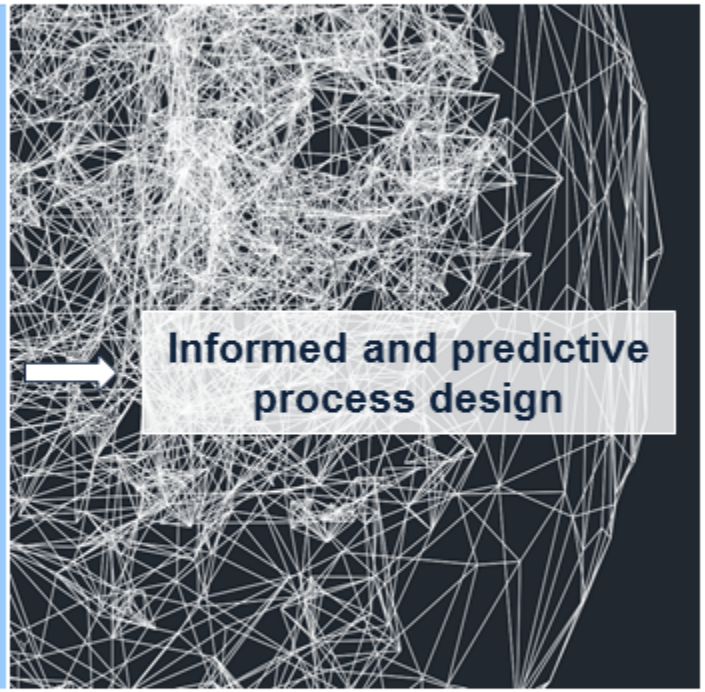
PARTEC

11 April 2019

CMAC – Future Manufacturing Hub

CMAC: Aim for integrated, continuous pharmaceutical MicroFactories supported by a predictive design framework to enable fast product and process development.





Process integration and control require reliable information on the product transformation for each process unit and a vast variety of pharmaceutical (intermediate) products with complex multi-dimensional solid attributes.

X-Ray Tomography of Pharmaceutics
Hardware and Data Collection

Scanning

Acquiring raw Data (2D, 14bit images) from sample.

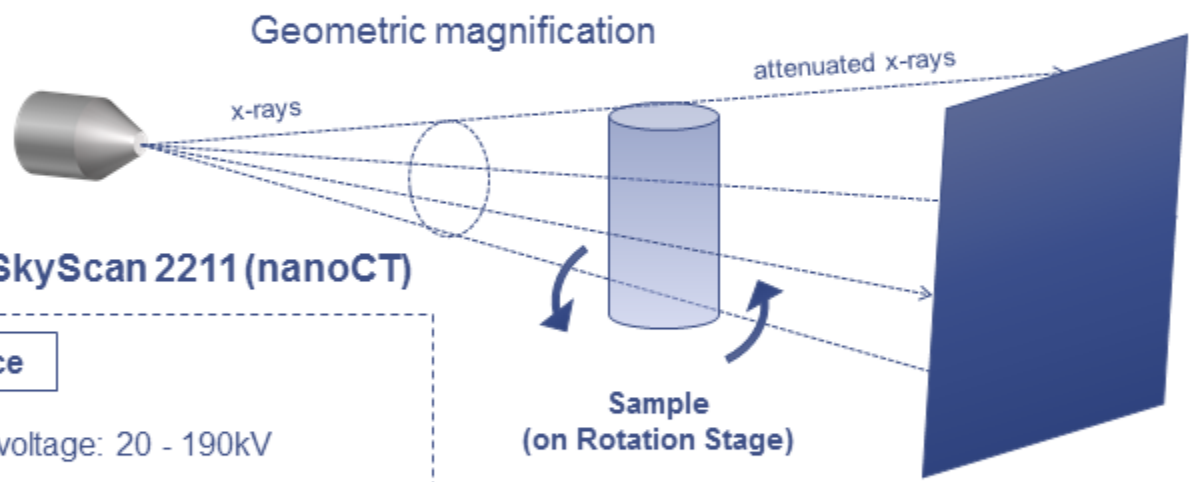
Reconstruction

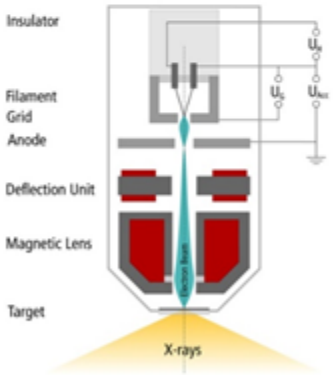
Transformation of 2D projections into a 3D-reconstruction of the sample

Analysis / 3D Rendering

Image analysis to extract desired sample information. 3D volume rendering to produce an interactive 3D model for visualisation.

SkyScan 2211 (nanoCT)





X-ray Source

Accelerating voltage: 20 - 190kV

Emission power: 10 W (Diamond window)

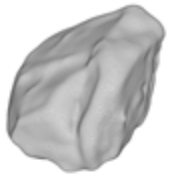
Transmission Target material: Tungsten

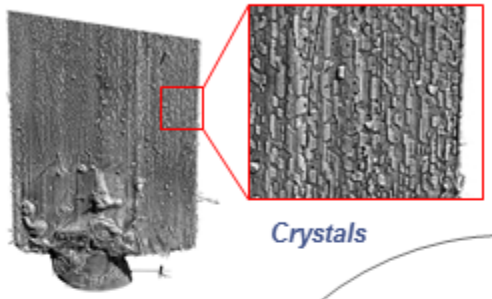
Beam spot size: nanomode 900nm, micromode 2um

Detector

- 11Mp CCD-Sensor
- CCD temperature stabilization
- central 4000x2670 pixel, 9um /pixel
- 14bit digitalization, 70dB dynamic range

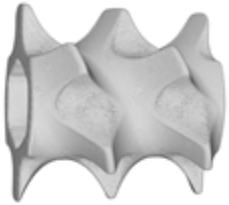
X-Ray Tomography of Pharmaceutics
Sample Overview





Crystals

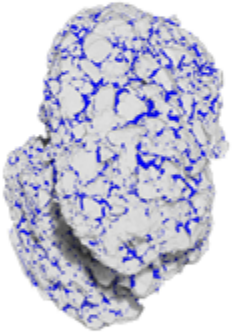
Extruder Elements



Spray dryer elements

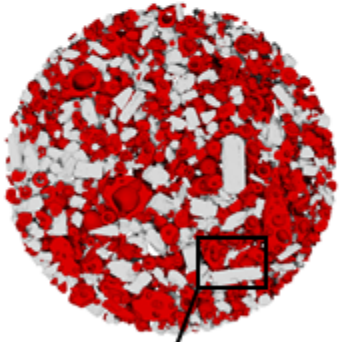
Particles

Granules

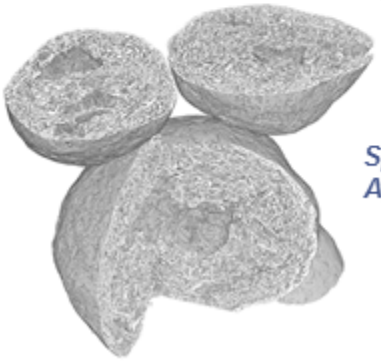


Single Particles	Mechanical Components
Powders	Formulated Systems

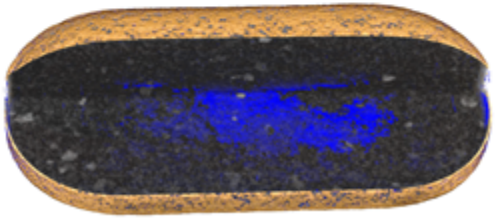
Tablets



Powder Blends



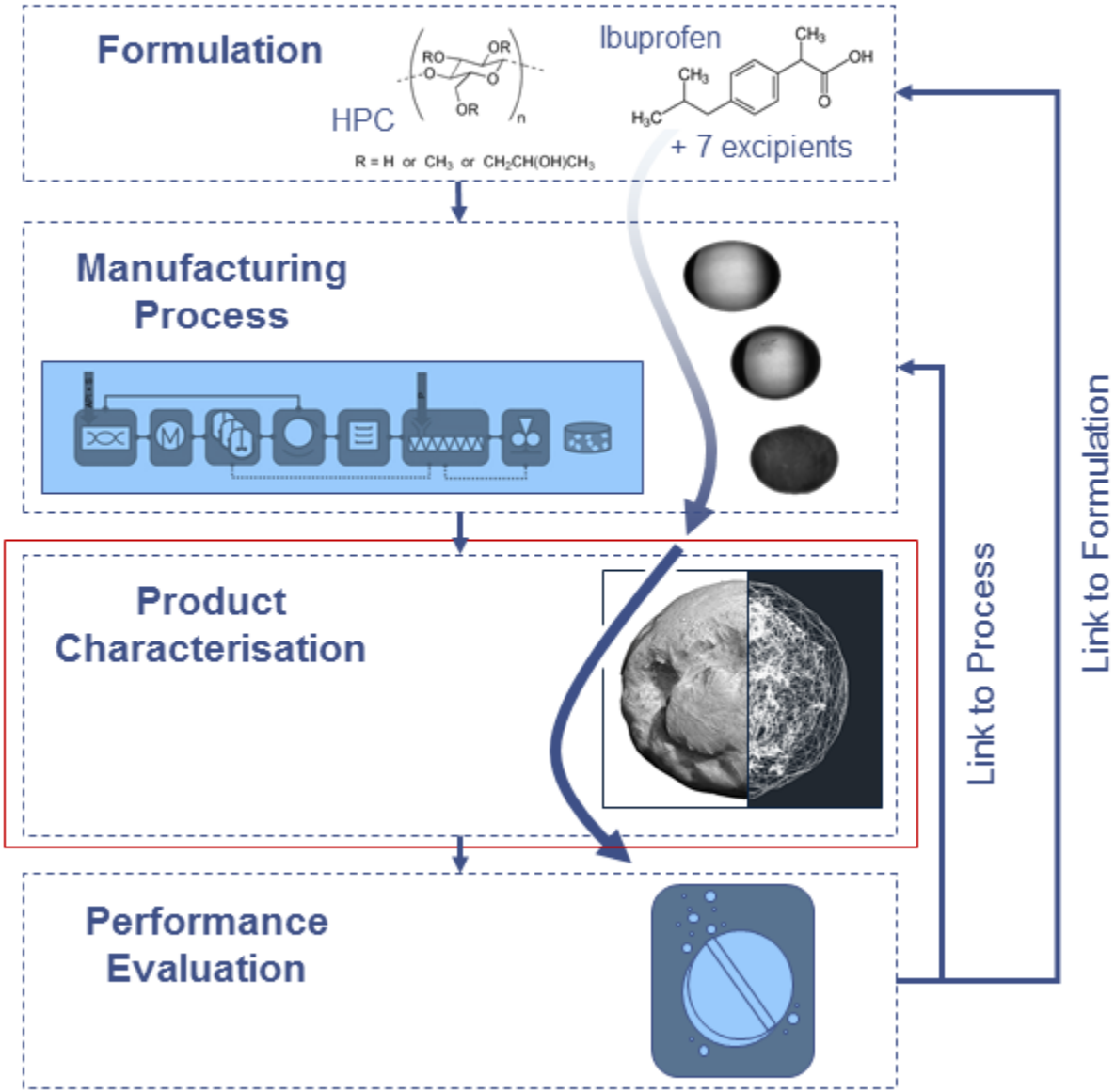
Spherical Agglomerates



Capsules

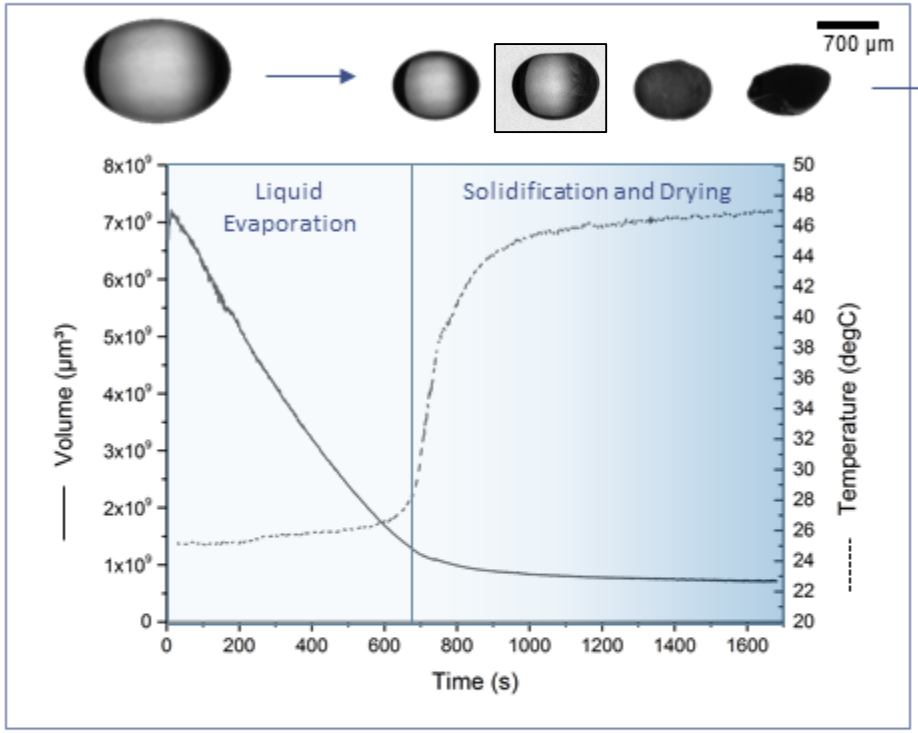
Doerr et al., Bruker micro-CT User Meeting (2017 & 2018)

X-Ray Tomography of Pharmaceutics
Motivation

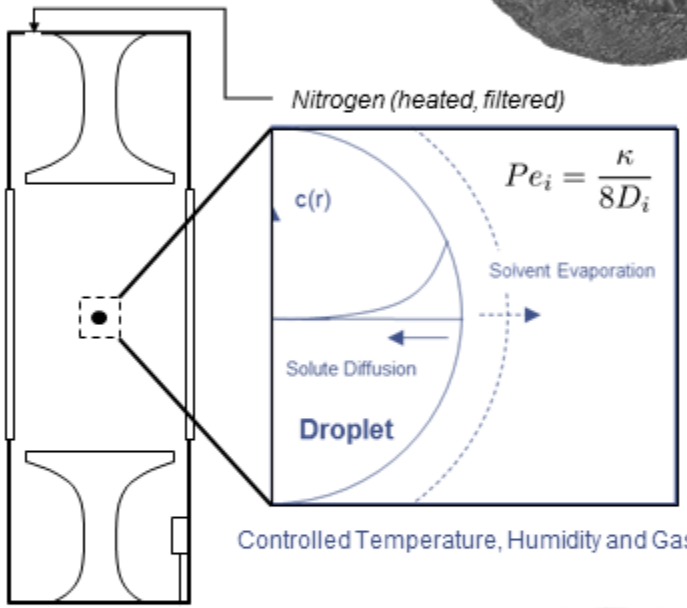


Capsules

XRT of Single Particles
Single Droplet Evaporation Experiments

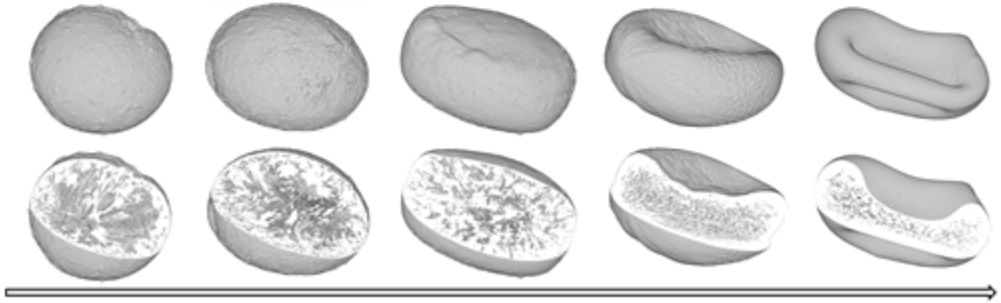


Investigation of Particle Structure



Controlled Temperature, Humidity and Gaseous Flow

Formulated particles with increasing Polymer Concentration



Particle Solid Phase
Particle Concave Surface Volume
Particle Porosity

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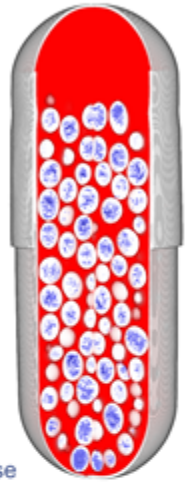
Doerr et al., 8th World Congress on Particle Technology (2018)
Doerr et al., Advanced Powder Technology (2018)

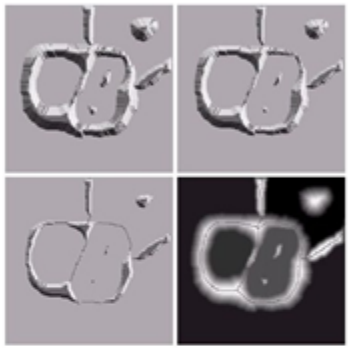
XRT of Multi-Particulate Systems
Object Segmentation

Commercial Capsules with formulated Pellets

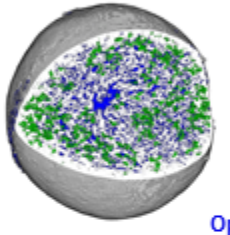


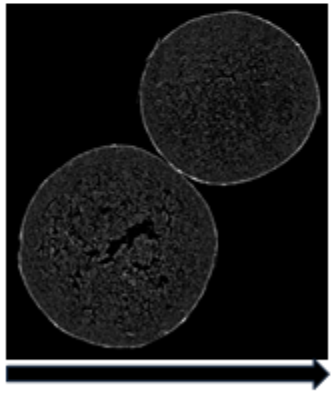
Watershed Transformation

R. Gonzalez and R. Woods. 2006. *Digital Image Processing*

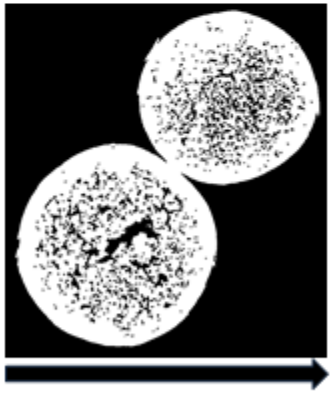


Extraction of Structural Descriptors of the primary Particle





8-bit Cross-sections



Binary Image

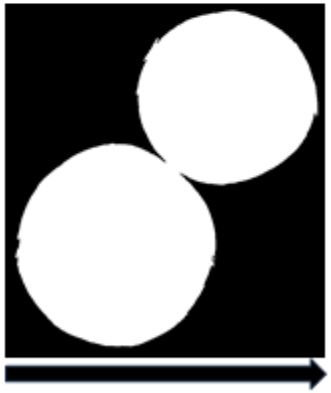
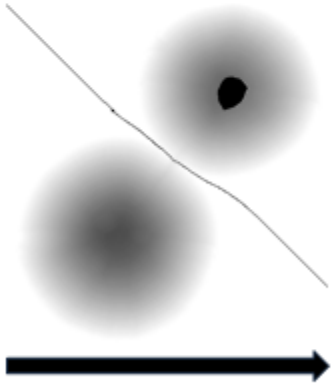
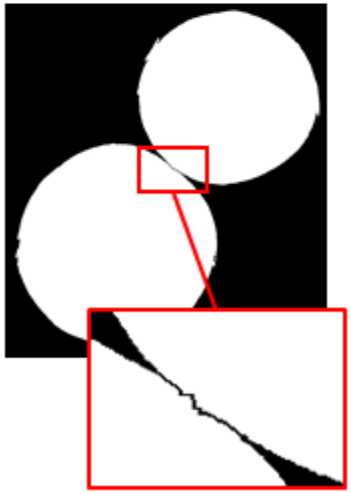


Image ROI

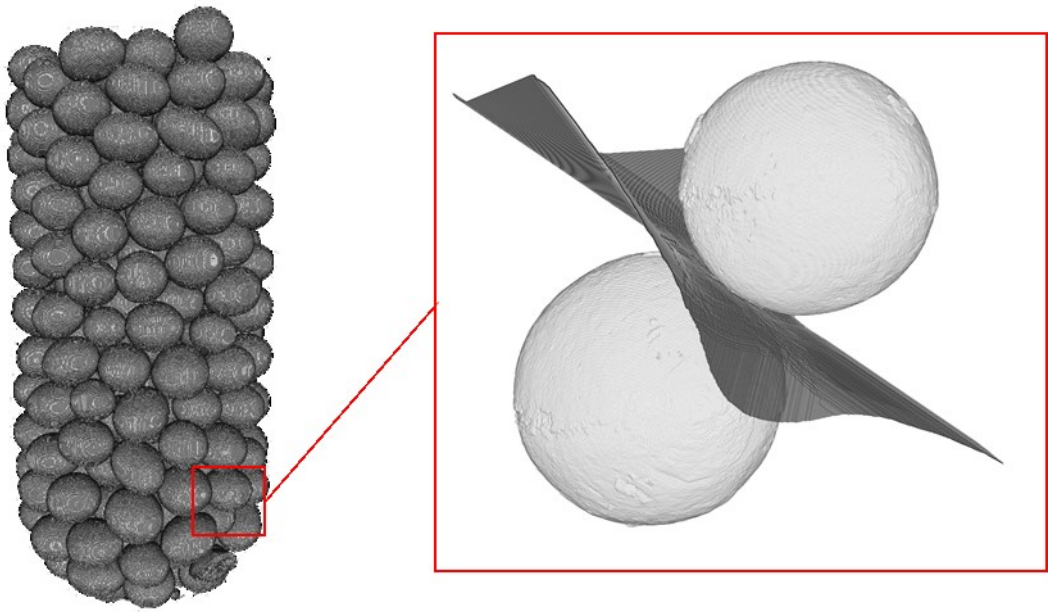


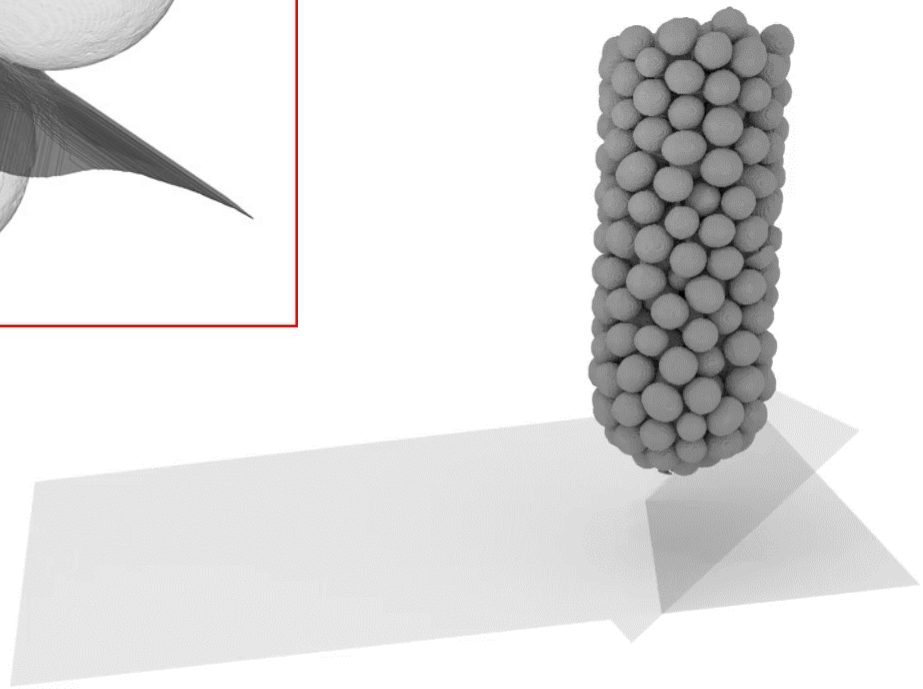
Marker-Controlled Watershed Segmentation



Adapted from Doerr et al (manuscript under preparation)

XRT of Multi-Particulate Systems
Object Segmentation



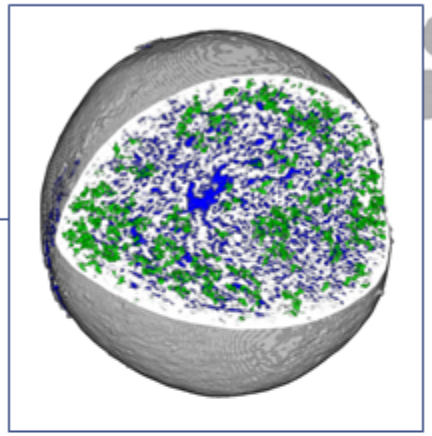


XRT of Multi-Particulate Systems
Particle Characterisation and Feature Extraction

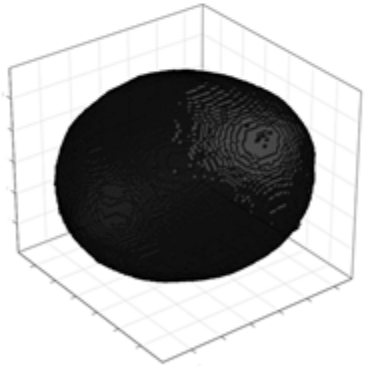
Particle Features (n > 200):

- Particle Solid Phase Volume
- Particle ROI Volume
- Particle 3D Convex hull Volume
- Open Porosity
- Closed Porosity
- Solidity
- Euler Number
- Extent
- Sphericity
- Eccentricity
- Aspect Ratio
- Particle Shape Fitting (Sphere, Half- Sphere, Ellipsoid, Cube, Rectangle)
- Orientation (Euler angles)
- Particle Open Surface Area
- Particle Closed Surface Area
- Particle Surface Roughness
- Particle Surface Buckling
- Particle Size (Feret, SphereEqv.)
- Fourier Shape Descriptors
- Hu Moments
- Zernike Moments

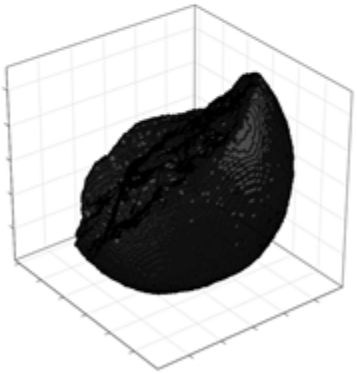
…



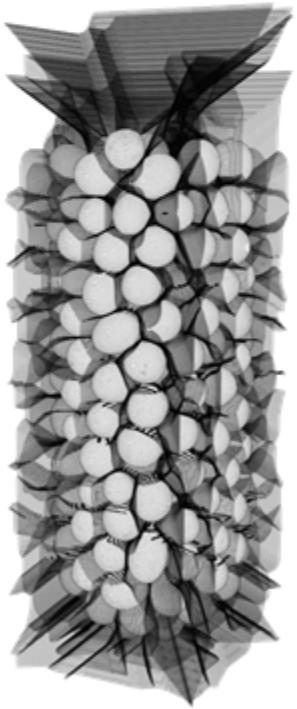
Open Porosity
Closed Porosity



Class 1: non-broken pellets

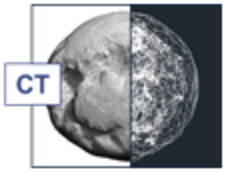


Class 2: broken pellets



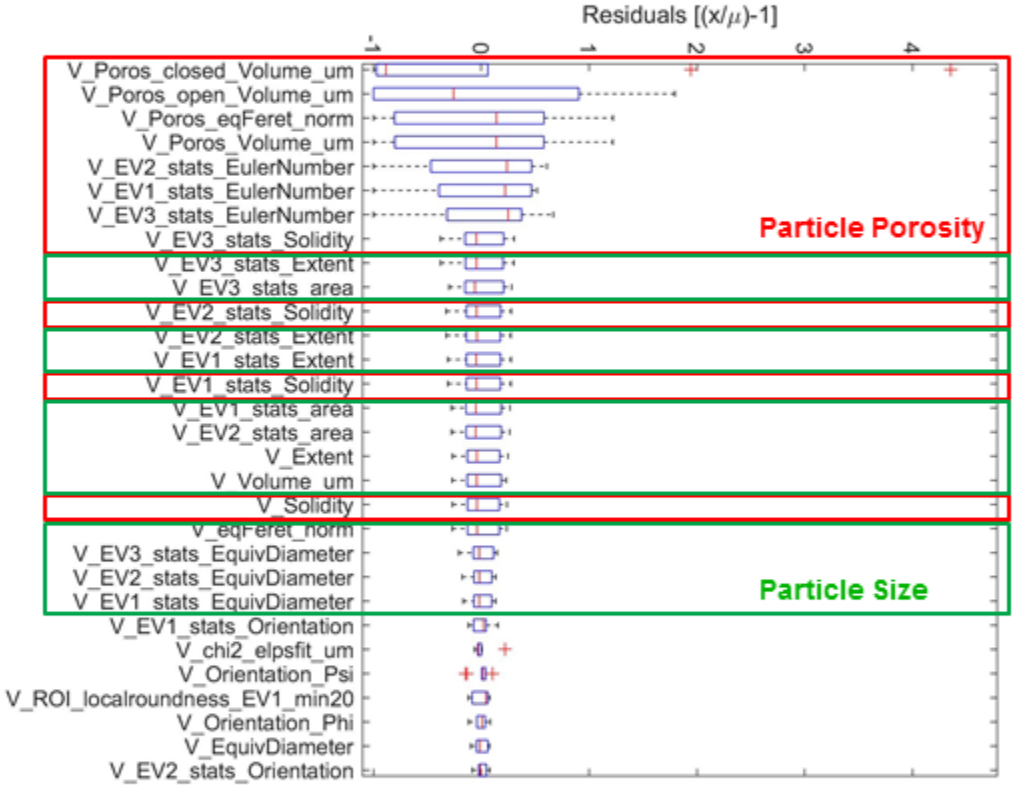
Adapted from Doerr et al (manuscript under preparation)

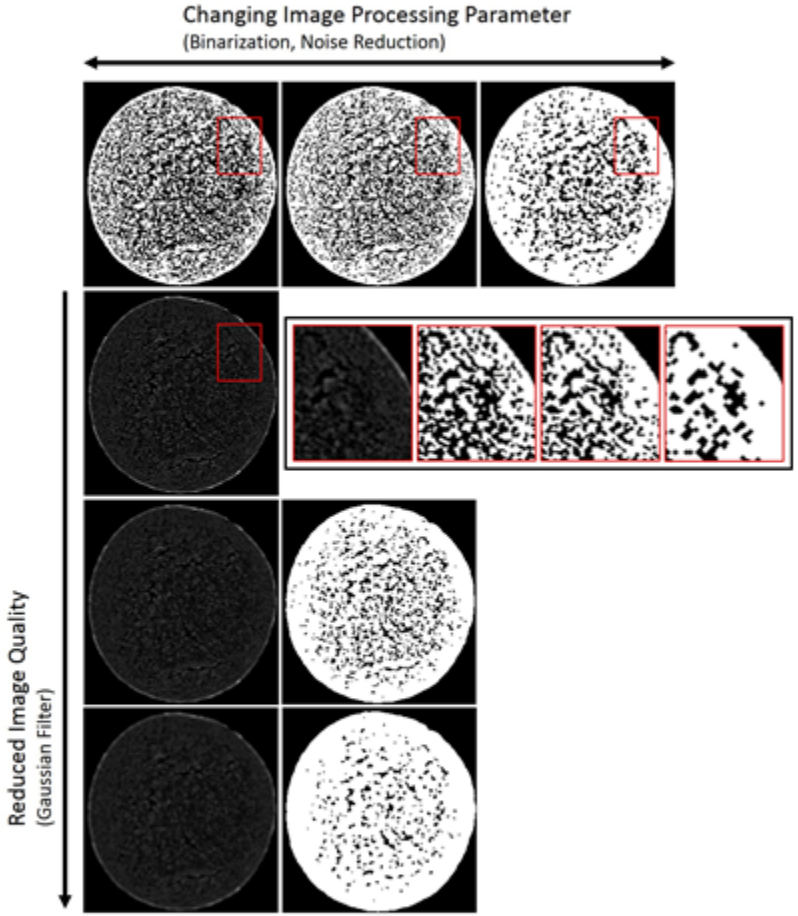
XRT of Multi-Particulate Systems
Feature Selection – Sensitivity Analysis



Sensitivity Analysis Response:

assessing raw XRT image quality, image processing parameter



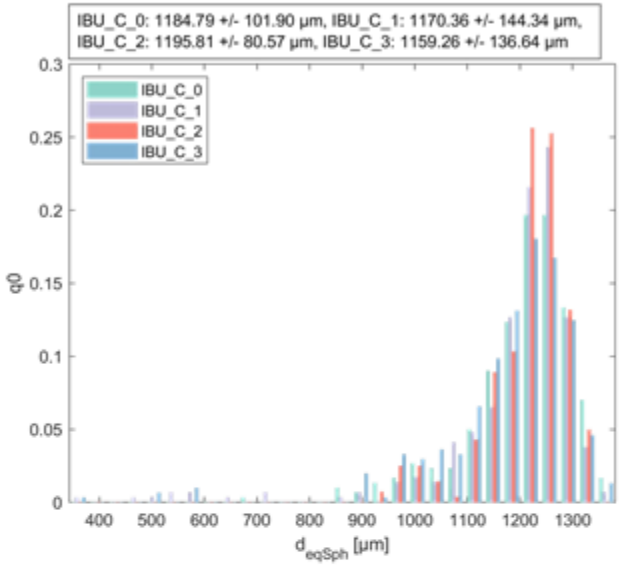


Object porosity features with the highest sensitivity for changes in XRT data quality and image processing parameters.

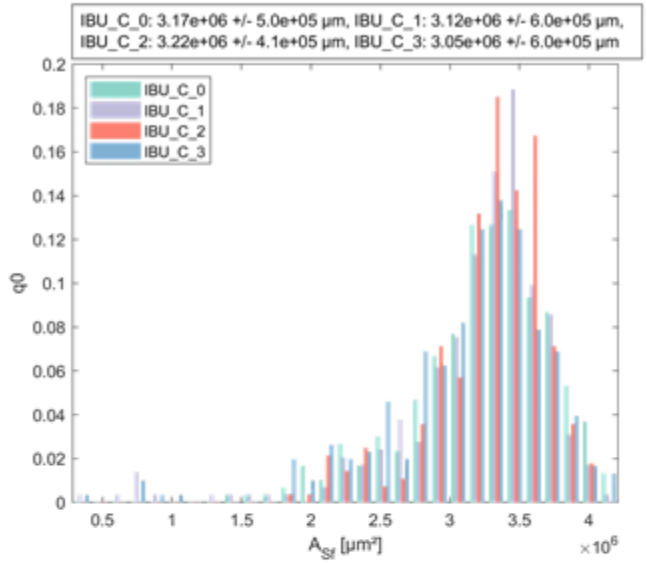
Adapted from Doerr et al (manuscript under preparation)

XRT of Multi-Particulate Systems
Feature Selection – Sensitivity Analysis

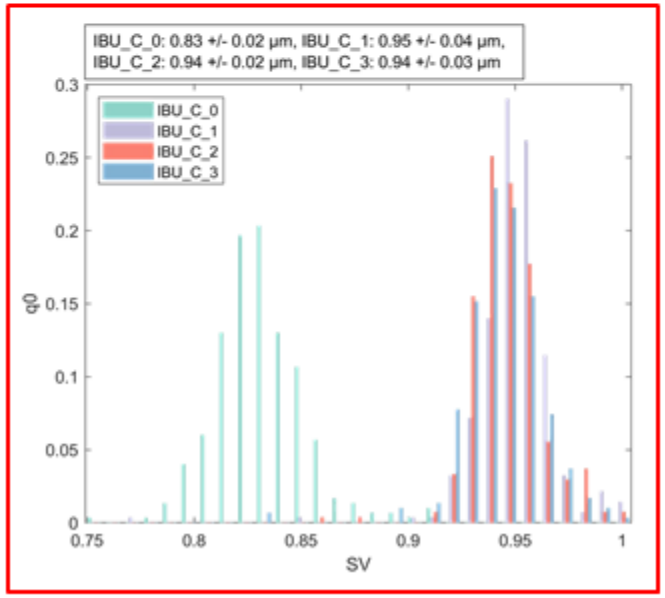
Equivalent Sphere Diameter



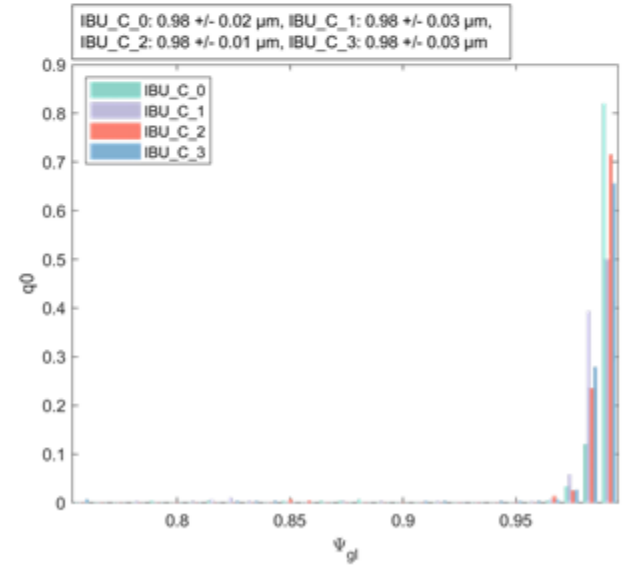
Surface Area



Solidity (V/V_ROI)

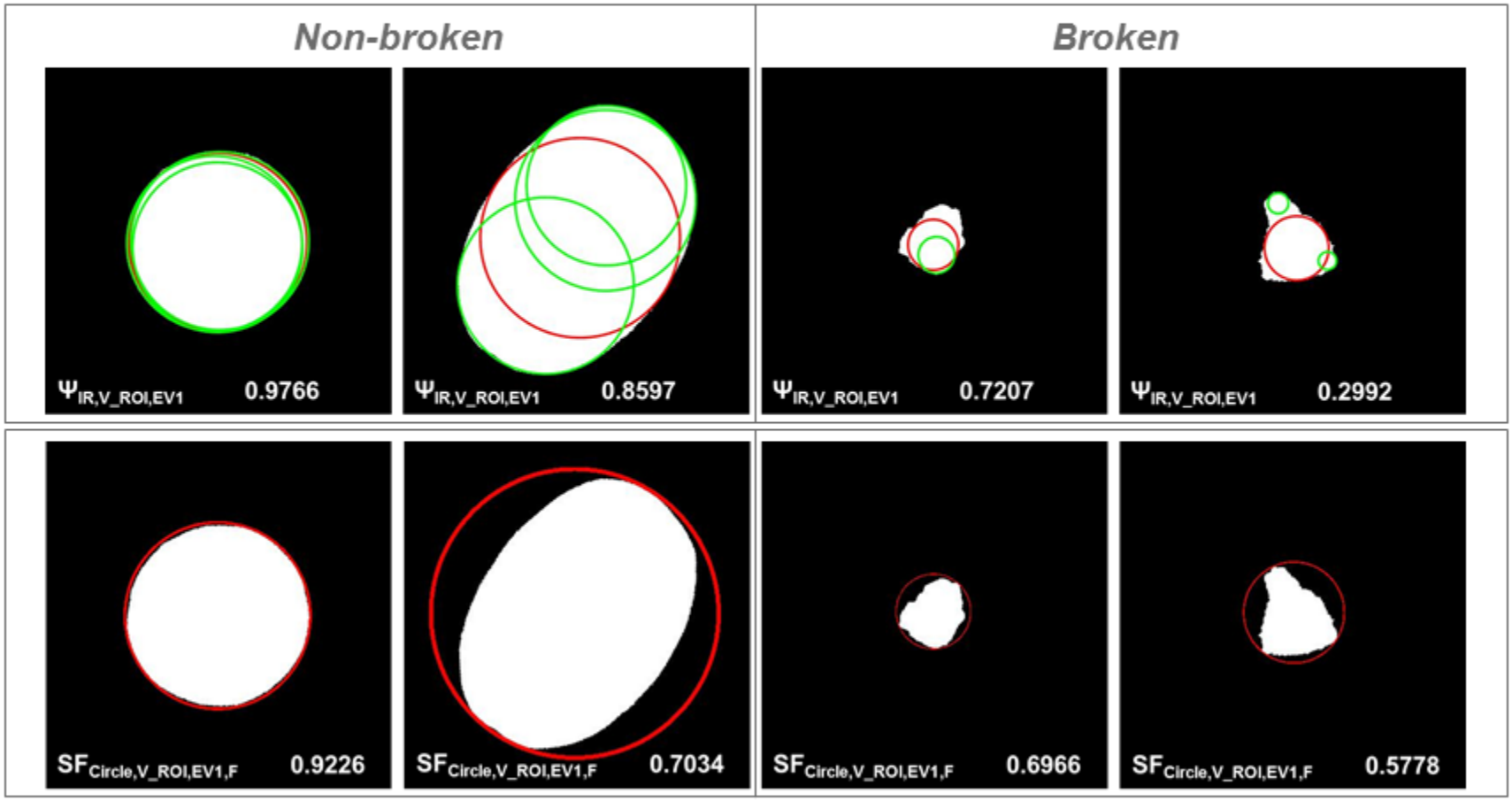


Sphericity (~V/A)



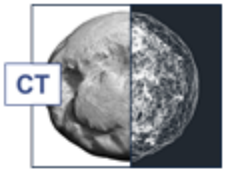
XRT of Multi-Particulate Systems
Feature Selection – Shape Features

ReliefF Feature Selection: local roundness (rank 1), circle shape fitting (rank 2)

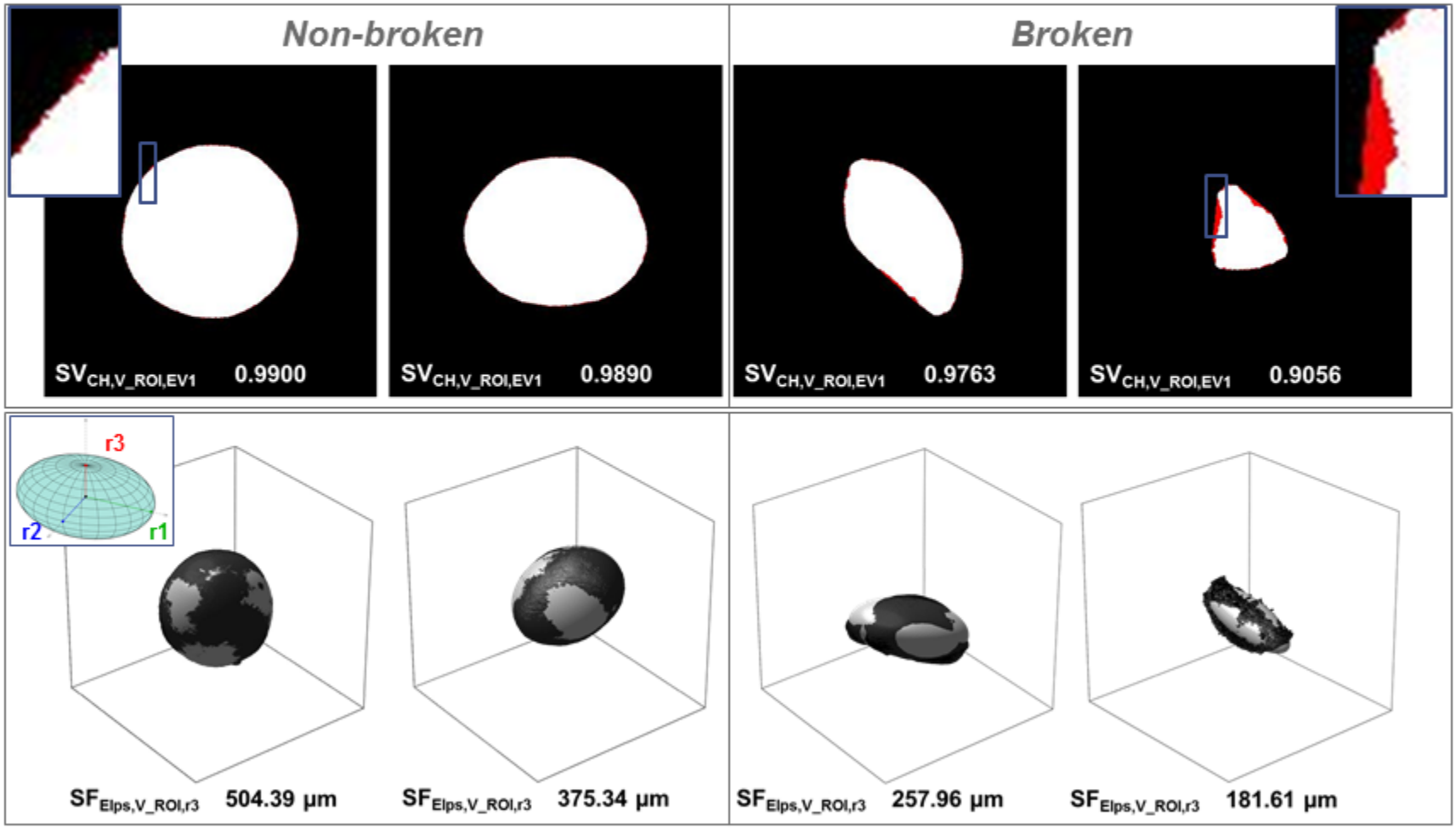


Kira &Rendell, AAAI-92 Proceedings (1992), Kononenko et al., Applied Intelligence (1997), Robnik-Šikonja et al., Machine Learning, (2003)

XRT of Multi-Particulate Systems
Feature Selection – Surface/Size Features



ReliefF Feature Selection: surface roughness (rank 22), ellipsoid axis length (rank 32)

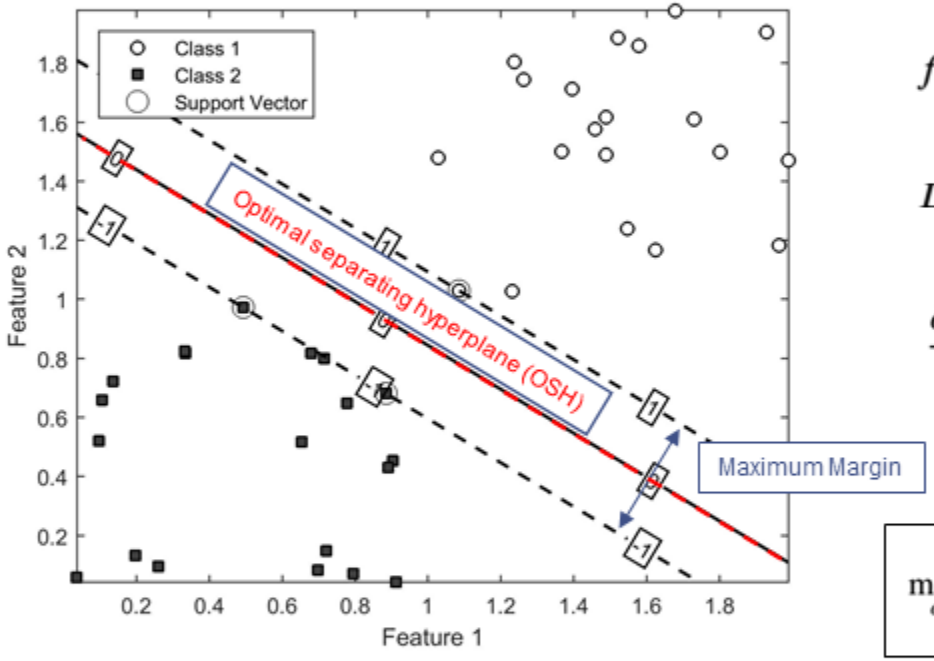


Kira &Rendell, AAAI-92 Proceedings (1992), Kononenko et al., Applied Intelligence (1997), Robnik-Šikonja et al., Machine Learning, (2003)

XRT of Multi-Particulate Systems
Feature-Based Object Classification

Support Vector Machines for Binary Classification

(Supervised Statistical Learning Approach)



Decision boundary

OSH Margin

$$f(x) = x \cdot w + b = 0$$

Support Vectors (Constraints)

$$L_P = \frac{1}{2}\|w\|^2 - \sum_i \alpha_i [y_i(x_i \cdot w + b) - 1]$$

$$\frac{\partial L_P}{\partial w} = w - \sum_i \alpha_i y_i x_i \,, \qquad \frac{\partial L_P}{\partial b} = -\sum_i \alpha_i y_i$$

at $L_P = 0$

Kernel

$$\max_\alpha \sum_i \alpha_i - \frac{1}{2}\sum_i \sum_j \alpha_i \alpha_j y_i y_j K(x_1, x_2) \quad \text{with} \quad \sum_i \alpha_i y_i = 0$$

Linear Kernel: $K(x_i, x_j) = x_i \cdot x_j$

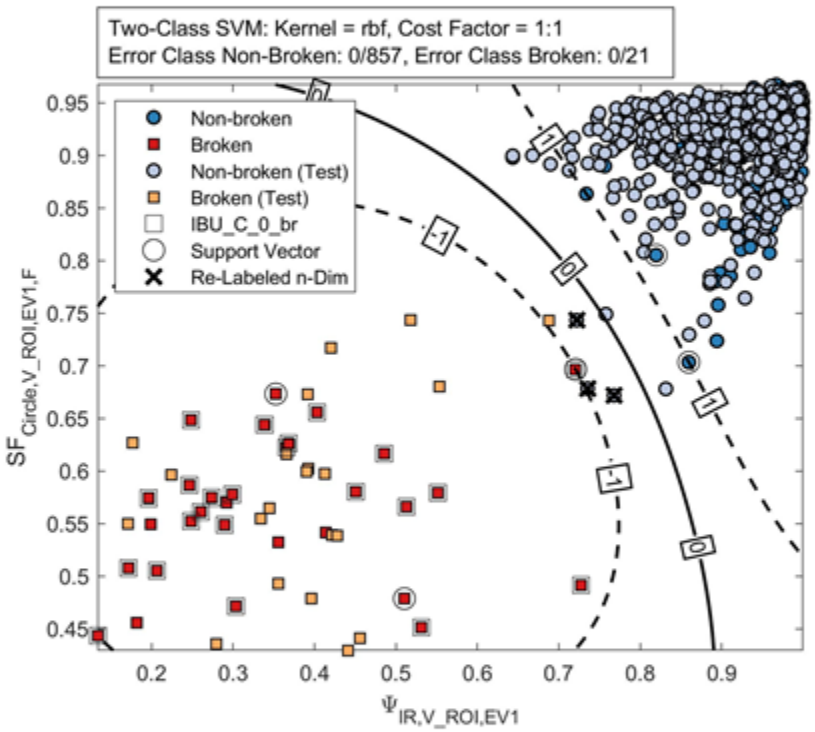
RBF Kernel: $K(x_i, x_j) = exp(-\frac{\|x_i - x_j\|^2}{2\sigma^2})$

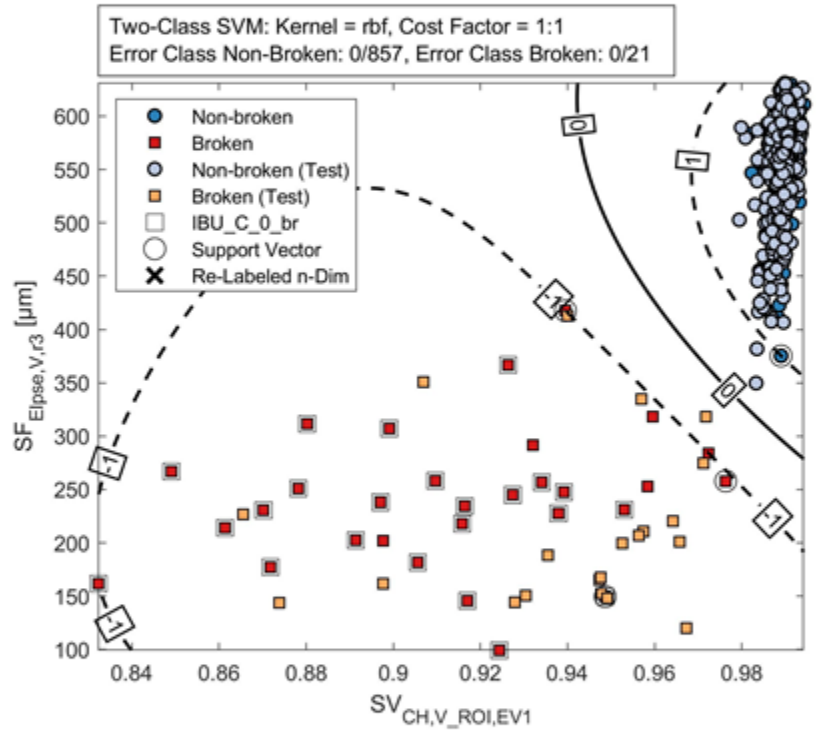
- **Support Vectors** define maximum OSH margin
- Non-linear decision boundaries with **Kernel trick**

Hastie, Springer (2008), Cristianini et al., Cambridge university press (2000)

XRT of Multi-Particulate Systems
Feature-Based Object Classification

Two-Class Support Vector Machine (hard margins)

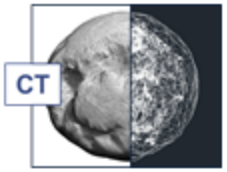




- OSH with hard margins **successful classification** of all test objects (*non-broken* vs. *broken*)

Adapted from Doerr et al (manuscript under preparation)

XRT of Multi-Particulate Systems
Feature-Based Object Classification



1

Class non-*broken*

$\Psi_{IR,V_ROI,EV1}$	0.860
$SF_{Circle,V_ROI,EV1,F}$	0.703
$SV_{CH,V_ROI,EV1}$	0.991
$SF_{Elps,V_ROI,r3}$	572.63 µm

2

Class *broken*

$\Psi_{IR,V_ROI,EV1}$	0.721
$SF_{Circle,V_ROI,EV1,F}$	0.700
$SV_{CH,V_ROI,EV1}$	0.949
$SF_{Elps,V_ROI,r3}$	149.56 µm

3

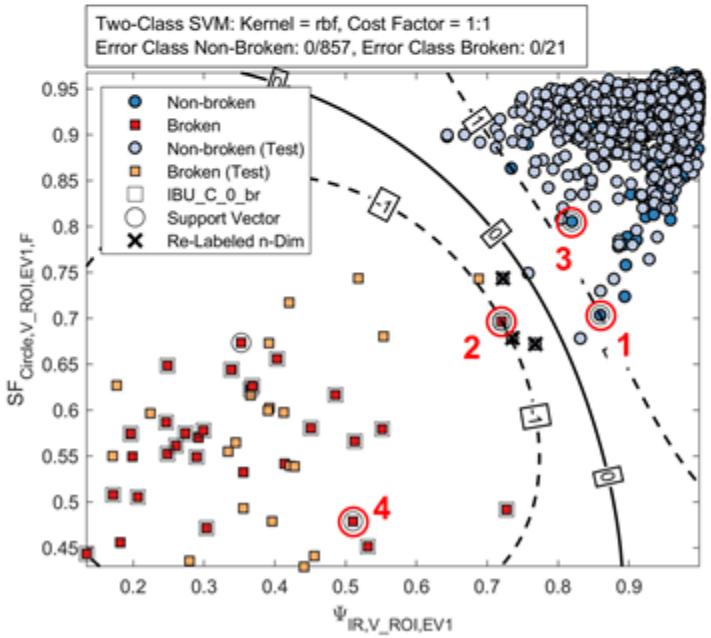
Class non-*broken*

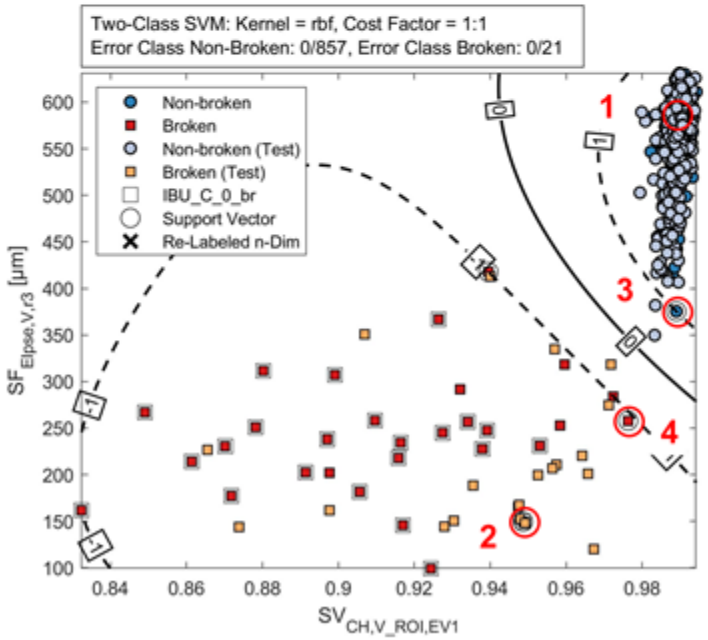
$\Psi_{IR,V_ROI,EV1}$	0.820
$SF_{Circle,V_ROI,EV1,F}$	0.805
$SV_{CH,V_ROI,EV1}$	0.989
$SF_{Elps,V_ROI,r3}$	375.34 µm

4

Class *broken*

$\Psi_{IR,V_ROI,EV1}$	0.510
$SF_{Circle,V_ROI,EV1,F}$	0.479
$SV_{CH,V_ROI,EV1}$	0.976
$SF_{Elps,V_ROI,r3}$	257.96 µm

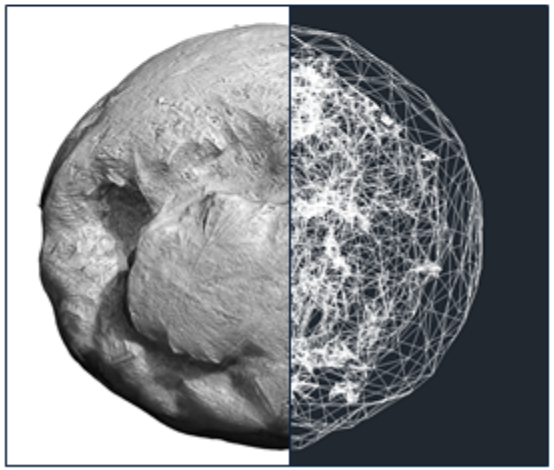


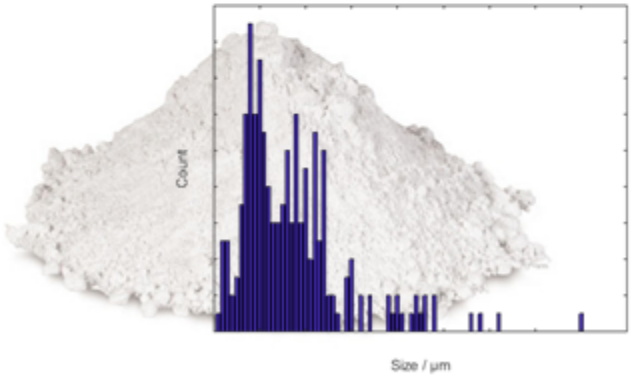


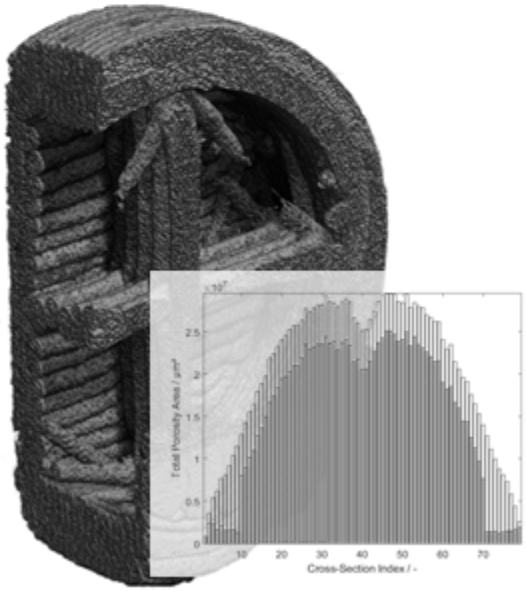
Adapted from Doerr et al (manuscript under preparation)

Conclusions

- CT analysis can be used to **non-destructively investigate the 3D structure** of a vast variety of solid pharmaceutical products with the potential to link extracted features to its final performance.
- **Quantitative analysis of multi-particle systems** requires the implementation of robust methods for volume segmentation. The **watershed transformation** can be applied to 'touching' multi-particle systems.
- The results from CT image processing and analysis can be used for **feature-based classification** models. This involved a **sensitivity analysis** and a **feature selection approach**.







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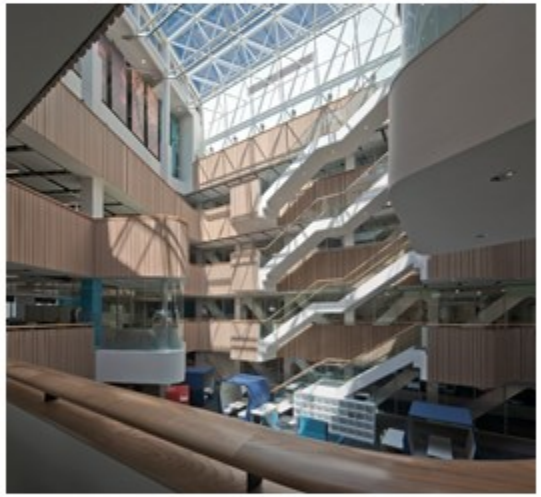

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