Novel Insight Into The Microstructure Of Fines-only Formulations Using X-ray Computed Tomography With Machine Learning

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Introduction

- There is on-going development of fines-only DPI formulations for achieving high-dose or high-efficiency pulmonary delivery.
- Characterising the microstructure of DPI formulations prior to aerosolization (pre-actuation) is important for the role that powder structure plays in air-permeability and particle dispersion during fluidisation.

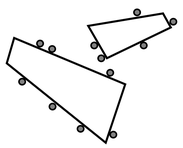
- X-ray Computed Tomography has recently emerged as a technique for characterising pre-actuated carrier-based formulations[1–3], however fines-only formulations are more challenging due to very small particle sizes.
- Machine-learning is increasingly used in microscopy for segmentation and classification, but this depends on the ground truth that can be established from the reconstructed virtual volume. Thus, the quality of the reconstructed data is critical.
- In this work, we show how machine-learning reconstructions increase the quality of reconstructed data for fines-only formulations, opening doors to quantification & relation to functional performance.

Methods

- Micronized alpha lactose monohydrate (micLac: Lactohale 300, Dv50 = 3.08 µm, Dv90 = 8.00 µm) was donated by DFE Pharma (Germany).
- Micronized fluticasone propionate (micFP, Dv50 = 2.30 µm) was purchased from Coral Pharma (India).
- Three blends of micLac to micFP were each prepared at 4 g scale using the sandwich technique and then mixed using resonant acoustic mixing apparatus (Resodyn LabRAM II Mixer) at 70 G for 2 mins.
- micLac, micFP and blends were loaded into kapton tube sample holders for scanning.
- Scans were performed on a Zeiss Xradia Ultra 810 XRM laboratory instrument (Carl Zeiss Microscopy, USA), operating at 5.4 keV in phase contrast mode.
- Traditional reconstruction performed using the Filtered-back projection algorithm were performed using XRM-Reconstructor (Carl Zeiss Microscopy, USA).
- Machine-learning reconstructions were performed using a neural-networked based algorithm with the Advanced Reconstruction Toolbox (Carl Zeiss Microscopy, USA) [4].
  - Wavelet Texture Analysis was performed in 2D on the middle 400 slices of each volume using the wavelet toolbox in Matlab [5].
    - Virtual volumes were visualised using Dragonfly Pro (Object Research Systems, Canada), whilst principal component analysis was performed in R.

Discussion & Future Work

- Machine-learning reconstructions offer improved image fidelity, making different particle morphology identifiable.
- The clear separation in image texture of the machine-learning reconstruction allows appropriate ground truths to be established, which is the starting point for machine-learning based segmentation and classification.
- Work is underway to study a wider range of blends, with different API and different blend combinations.
- The clear improvement from machine-learning reconstruction opens opportunities for other inhalation formulation, such as carrier-based formulations and spray-dried formulations (see right).



Carrier-based formulations

- Nanoscale XCT could be used to understand the interface of carrier and micronized particles in 3D.

Spray-dried formulations

- Nanoscale XCT could be used to understand the 3D morphology, packing and interactions between spray-dried particles.

References

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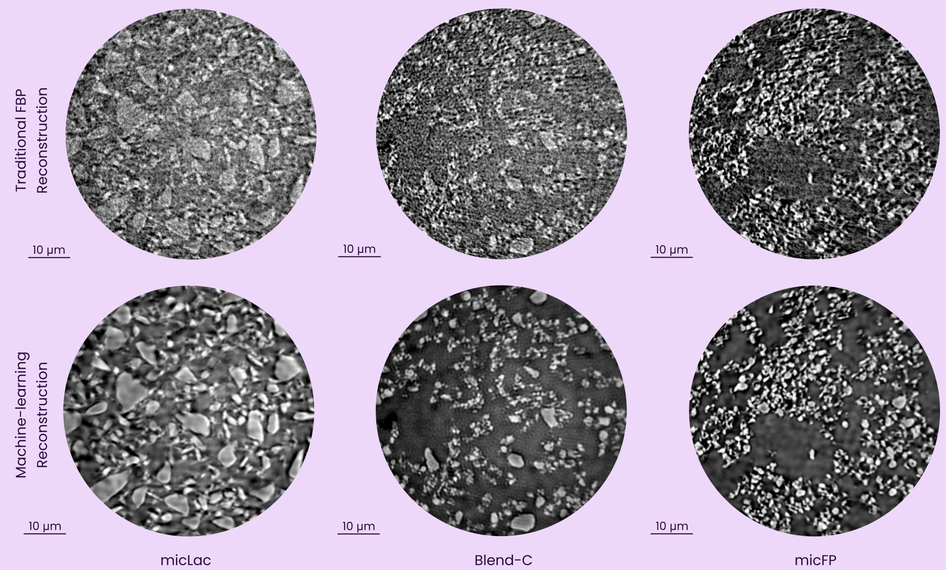
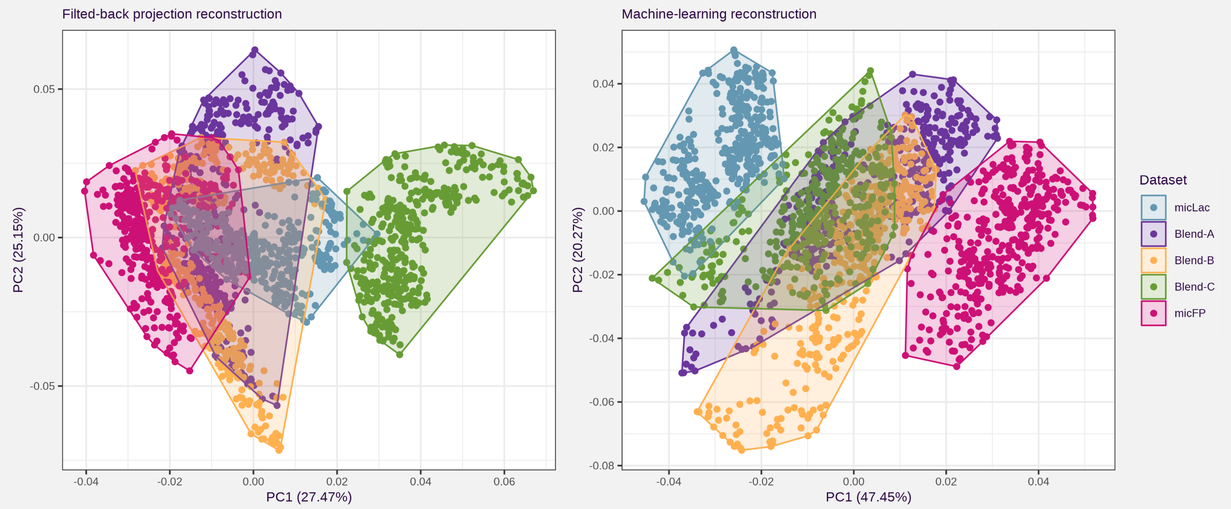
Reconstructed Data Results

- Cross-sectional slices shown on the right for both types of reconstructions.
- The traditional FBP reconstructions produce a lot of uncorrelated noise in the virtual volumes.
- This noise makes it difficult to distinguish between air and particles. Consequentially, it is difficult to determine the exact morphology of the different particulate materials, especially for smaller micLac and micFP particles.
- The machine-learning reconstruction algorithm determines uncorrelated noise.
- Thus, virtual volumes display less noise, meaning that particle edges are more clearly defined and morphology of individual particles can be determined.
- The machine-learning reconstruction of the blend highlights the contrast in image fidelity between reconstruction methods.
- Machine-learning reconstruction of blend allows individual particles to be identified, and their morphology to be assessed qualitatively.



Wavelet Texture Analysis Results



- Traditional reconstruction was not able to distinguish blends from raw material
- First two principal component show reasonable representation of the data.
- Machine learning reconstruction shows separation between the micLac and micFP, with the blends lying in the space in between
- First two principal components show excellent representation of the data.