AI-Assisted Optimisation of Oral Solid Dosage Form Development: Unlocking Efficiency and Precision

CMAC – Centre for Continuous Manufacturing and Advanced Crystallisation

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Digital Medicines Manufacturing (DM²)

We use **computational modelling** and **artificial intelligence (AI)** to develop an autonomous digital workflow for drug product manufacturing and testing system. The **hybrid machine** uses critical raw material attributes (CMAs) and critical process parameters (CPPs) to predict mixture properties and tablet critical quality attributes (CQAs).

The **model-based optimisation framework** (Figure 1) smartly designs the experiments to drive the self-optimising formulation and process system and update the **hybrid machine** (Figure 2) to learn from the experiments performed.

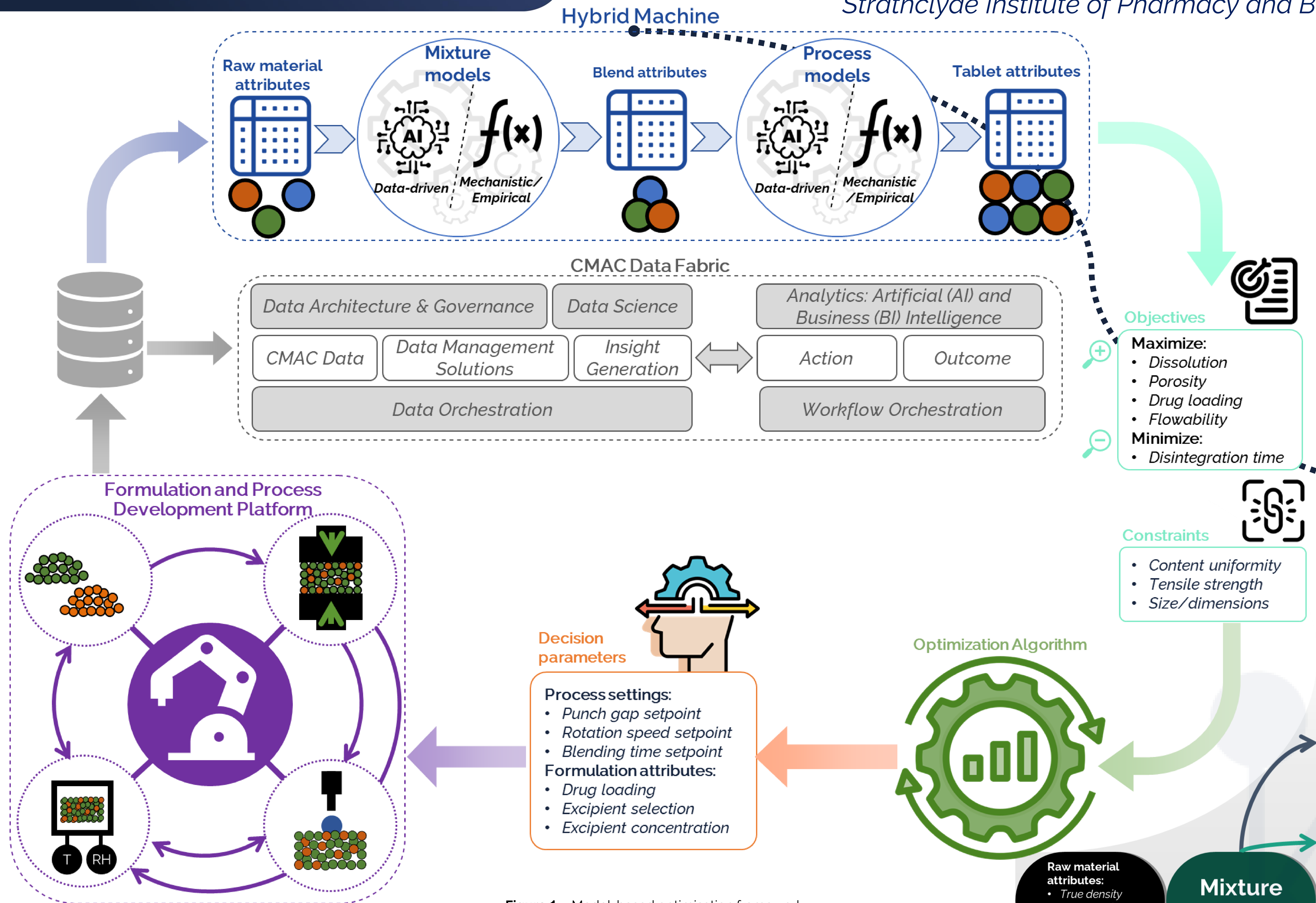

Figure 1 – Model-based optimisation framework.

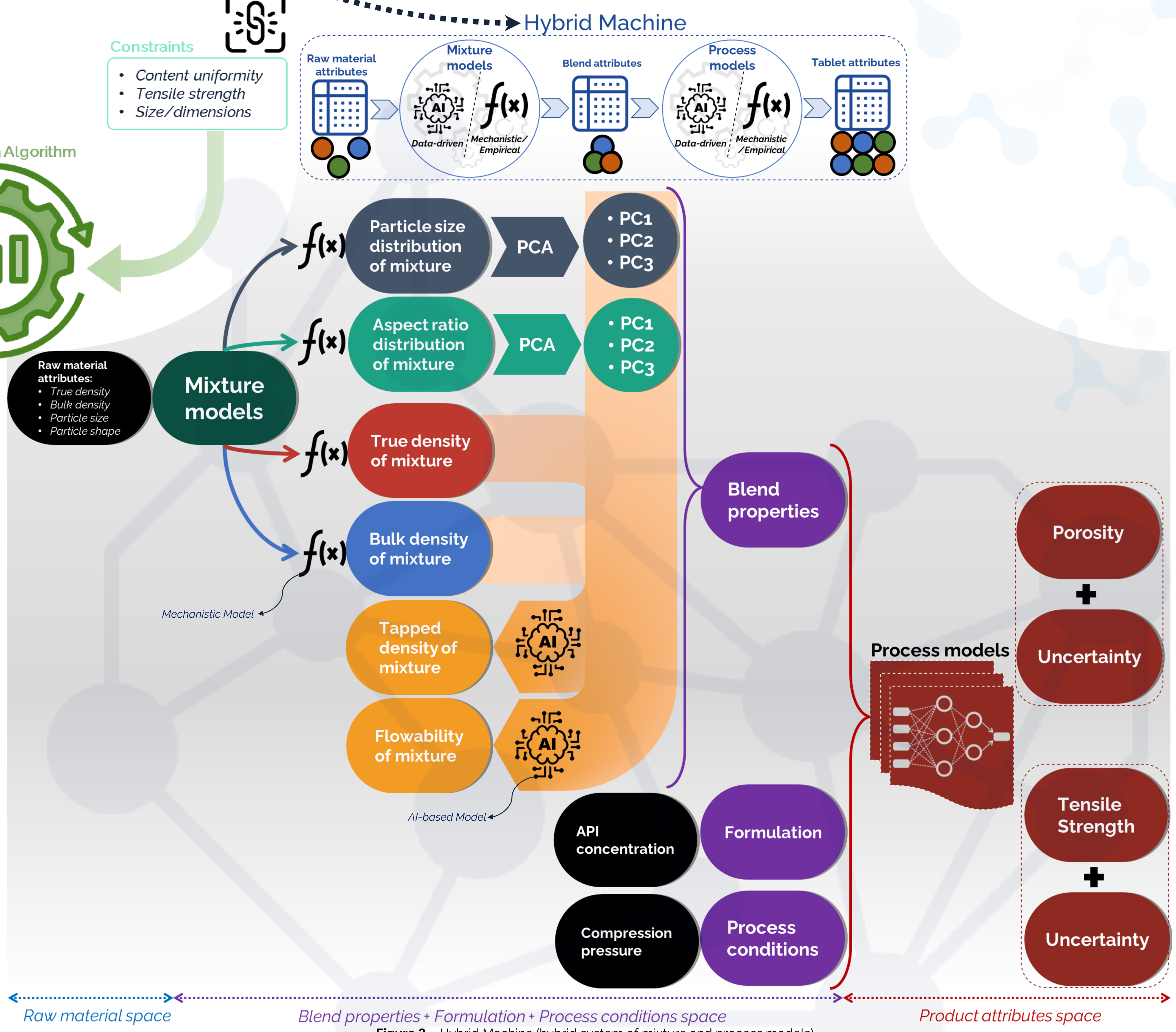

Figure 2 – Hybrid Machine (hybrid system of mixture and process models).

Hybrid Mixture Models

$f(x)$ Particle Size & Shape *(Probabilistic Model)*

$$n_i^{mix} = \sum_{j=1}^{K} \lambda_j(C_j, \rho_j^{true}) \times n_i^j$$

λ: Probability of membership
C: Mass fraction
ρ^{true}: True density
K: Number of components

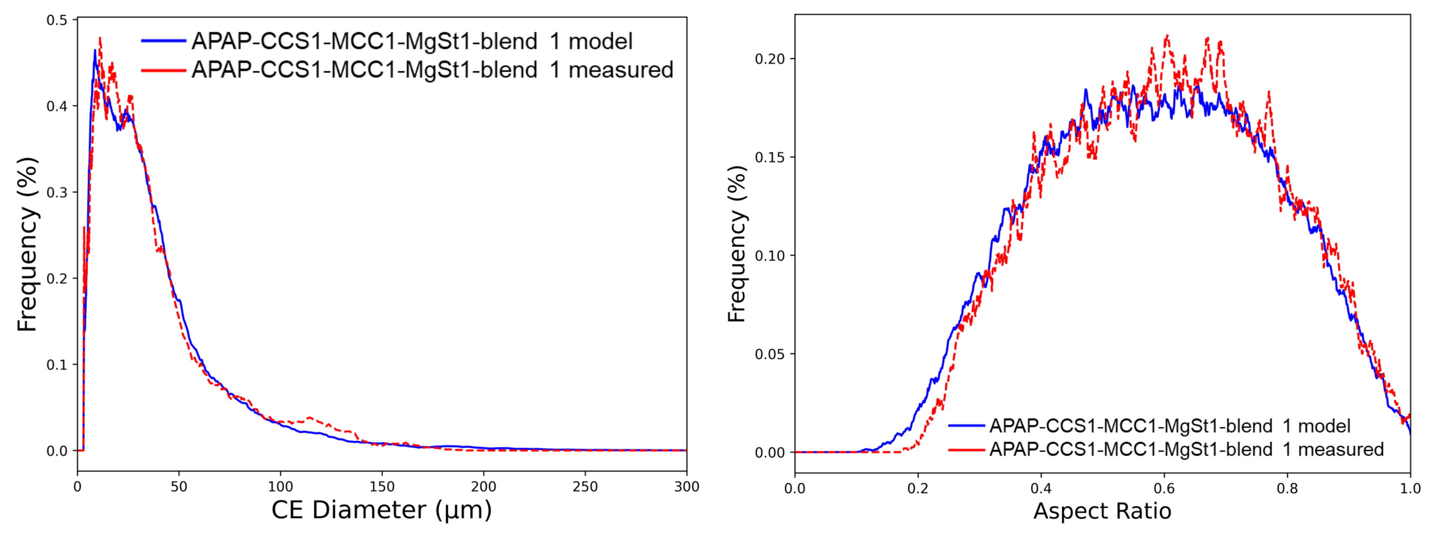

Figure 3 – Prediction performance of particle size and shape probabilistic model vs. measured distributions

Principal Component Analysis (PCA) – *Dimensionality Reduction*

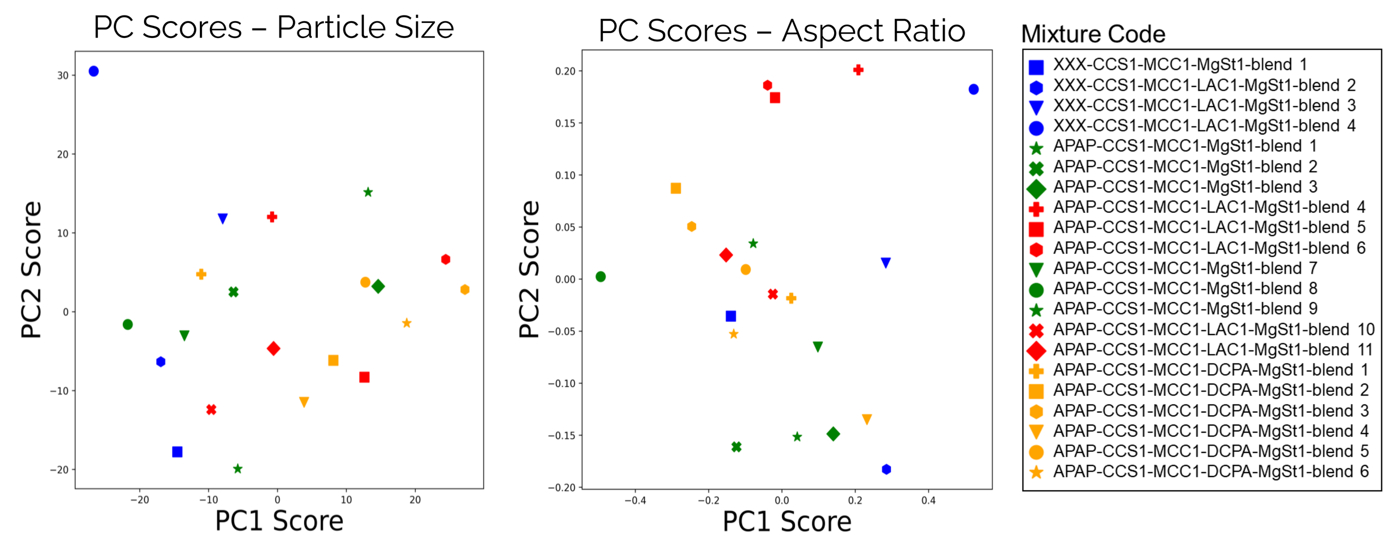

Figure 4 – Principal scores of particle size and shape distributions for different mixtures predicted by probabilistic model.

$f(x)$ True Density *(Harmonic Mean)*

$$\rho_{mix}^{true} = \frac{\sum_i^K C_i}{\sum_i^K C_i/\rho_i^{true}}$$

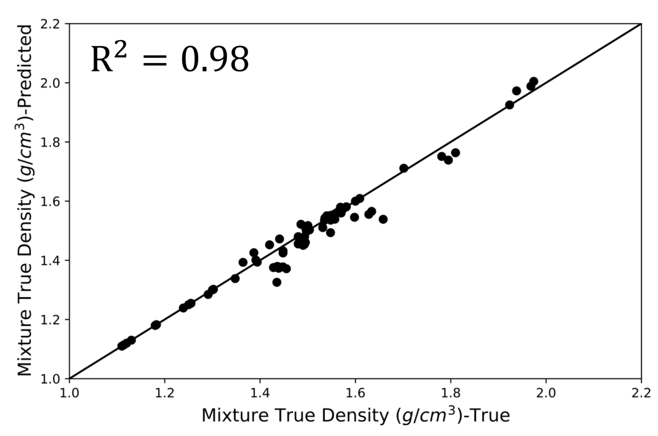

Figure 5 – Prediction performance of true density mixture model.

$f(x)$ Bulk Density *(Mass-weighted Mean)*

$$\rho_{mix}^{bulk} = \frac{\sum_i^K C_i \rho_i^{bulk}}{\sum_i^K C_j}$$

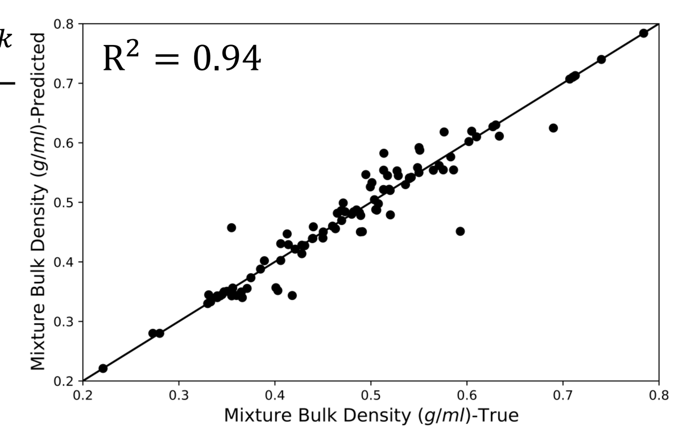

Figure 6 – Prediction performance of bulk density mixture model.

Tapped Density modelling using machine learning regression models

- eXtreme Gradient Boosting (XGBoost)
- Gradient Boosting Regression (GBR)
- Support Vector Regression (SVR)
- Random Forest (RF)

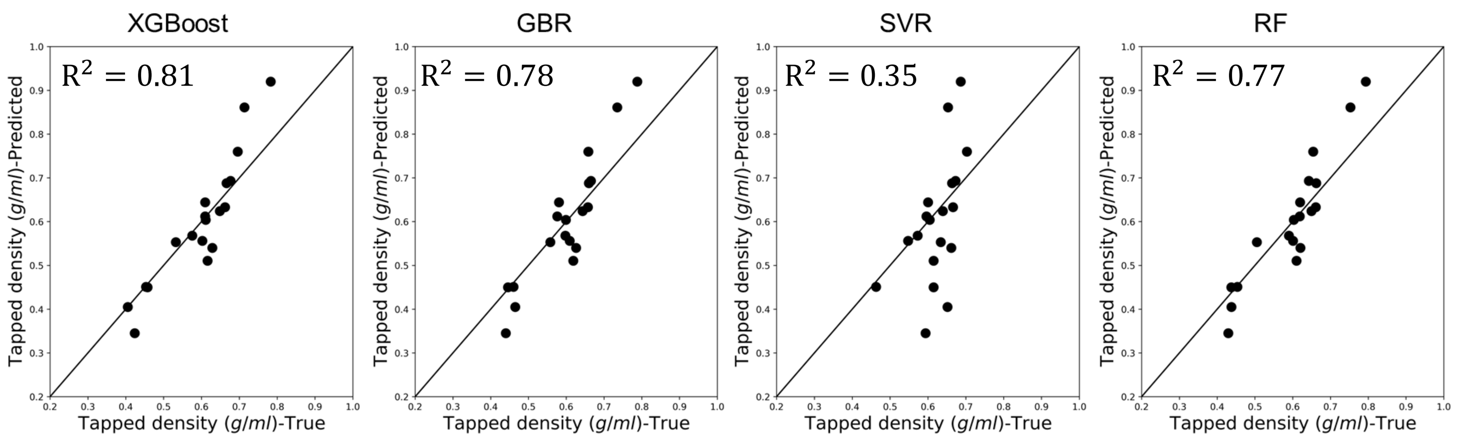

Figure 7 – Prediction performance of tapped density mixture models.

Flowability modelling using random forest regression to predict flow function coefficient (FFC) of powder mixtures.

- Model-based uncertainty quantification (UQ) to estimated relative standard deviation (RSD) of predicted FFC values.
- Results confirm prior experimental investigations on higher measurement uncertainty in free-flowing powders.

		Predicted			
		Cohesive	Easy-flowing	Free-flowing	Σ
True	Cohesive	24	0	0	24
	Easy-flowing	1	16	3	20
	Free-flowing	0	4	12	16
	Σ	25	20	15	60

Figure 9 – Classification performance of flowability mixture model.

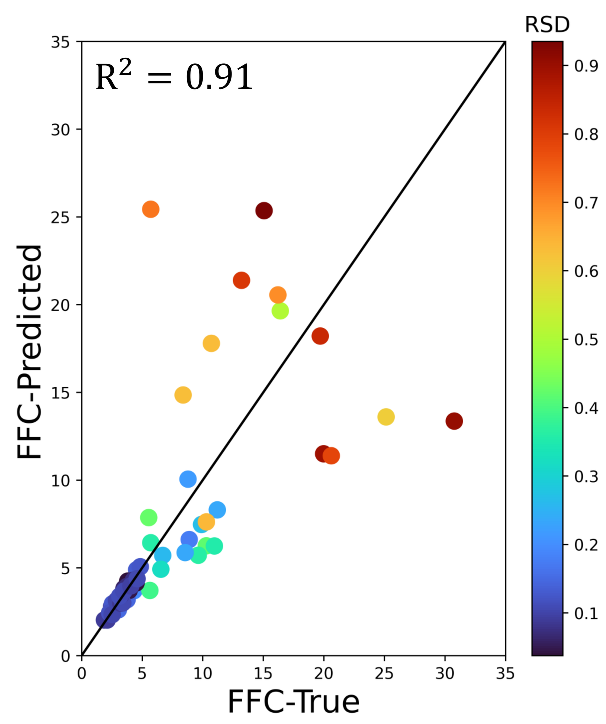

Figure 8 – Prediction performance of flowability mixture model. Colour bar shows relative standard deviation (RSD) of future predictions.

AI-Based Process Models

- ***Efficiency:*** Deep Neural Networks (DNNs) models were developed to predict porosity and tensile strength of directly compressed tablets using raw material properties, formulation, and process conditions, reducing the cost and time of blend/tablet characterization and testing.
- ***Precision:*** Ensemble learning was employed to develop multiple DNNs to predict the value and uncertainty of tablet porosity and tensile strength. The model-based uncertainty quantification (UQ) will help to predict the uncertainty of future predictions and inform next experiments to maximise the model accuracy while minimising the number of experiments.

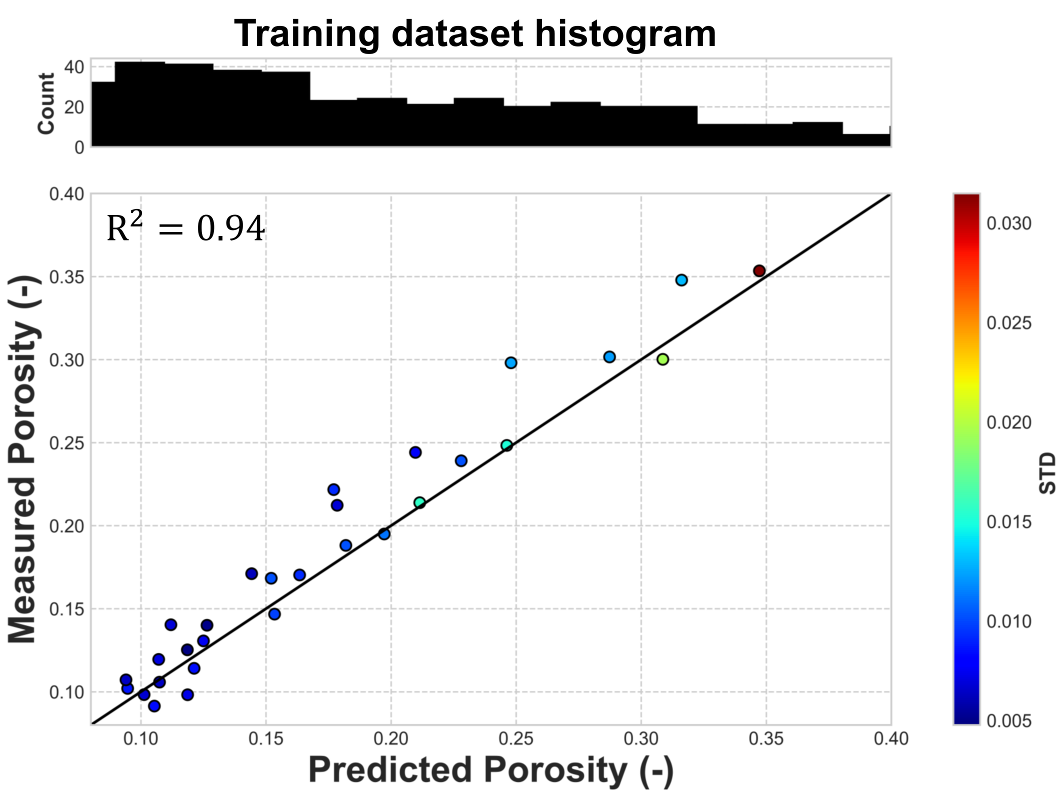

Figure 10 – Prediction performance of tablet porosity model. Colour bar shows standard deviation (STD) of future predictions.

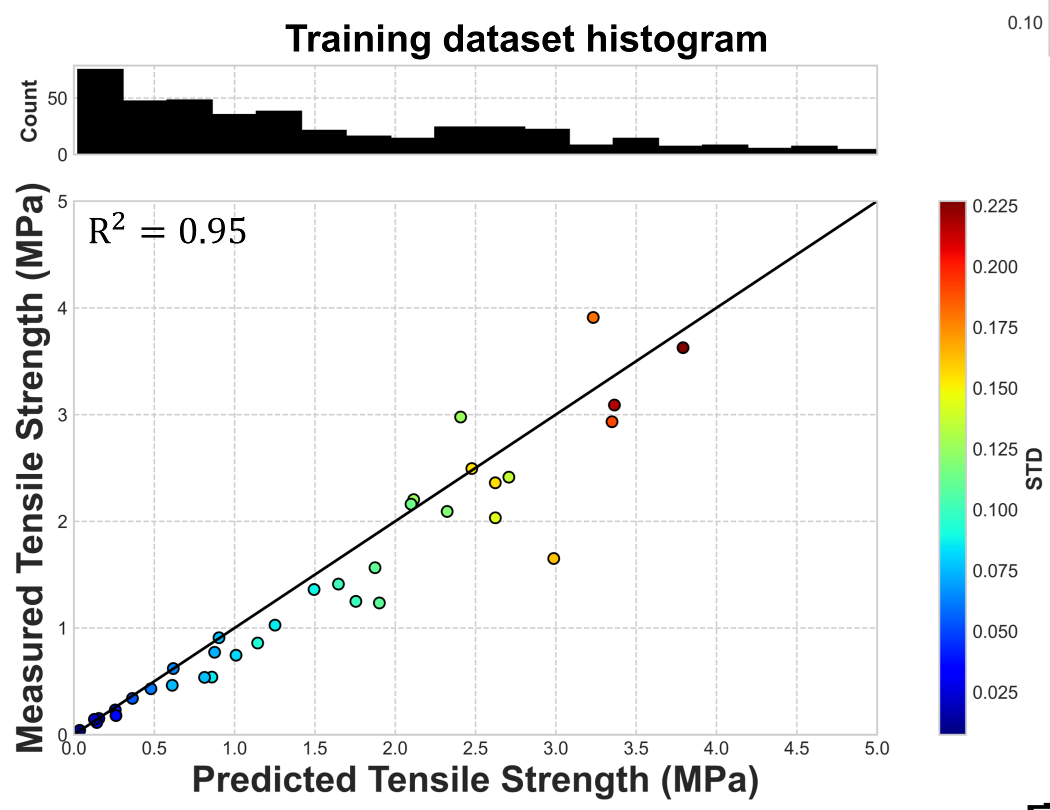

Figure 11 – Prediction performance of tablet tensile strength model. Colour bar shows standard deviation (STD) of future predictions.

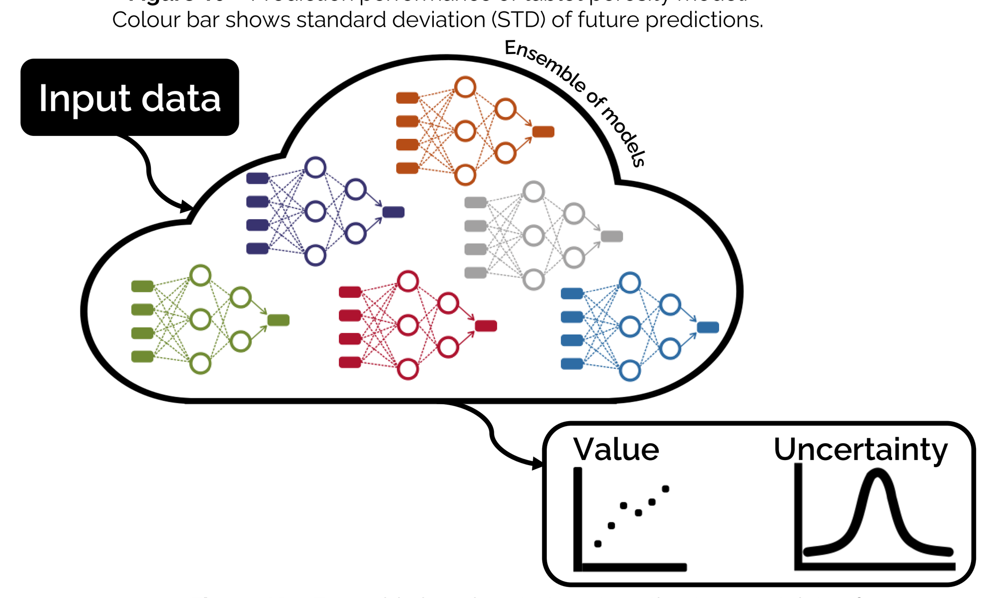

Figure 12 – Ensemble learning strategy to estimate uncertainty of future predictions.

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