Model Driven Design of Formulated Products

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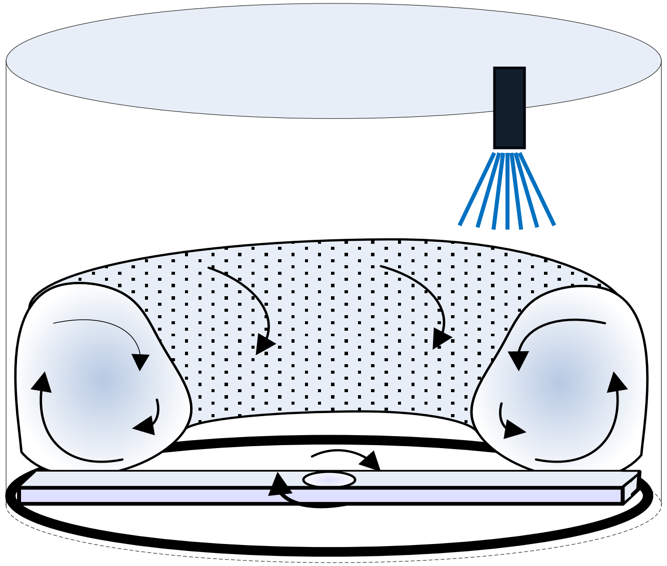
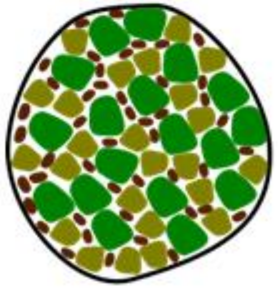
Process-product relationship in disintegration of granules

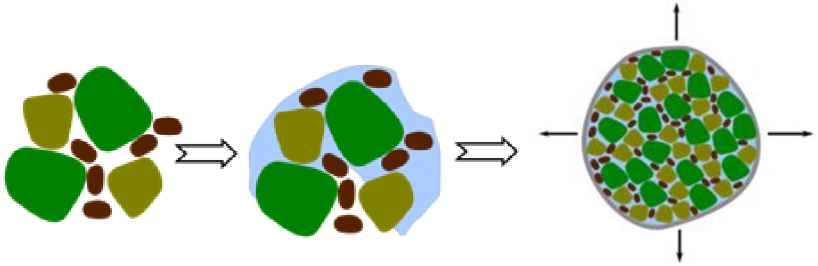
High Shear Wet Granulation Process Model

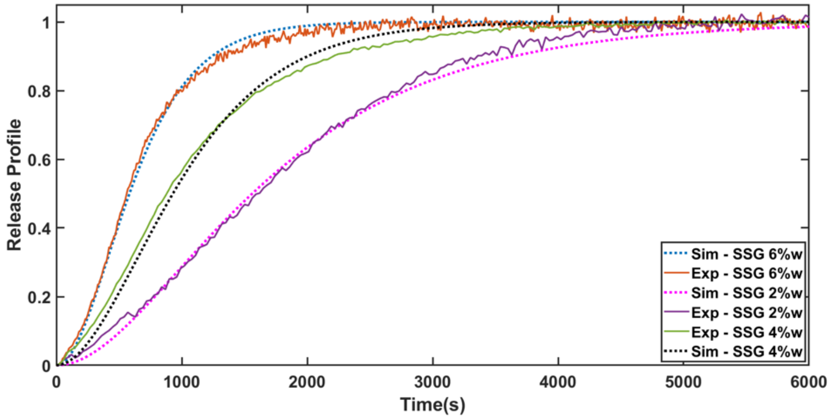


Product Properties



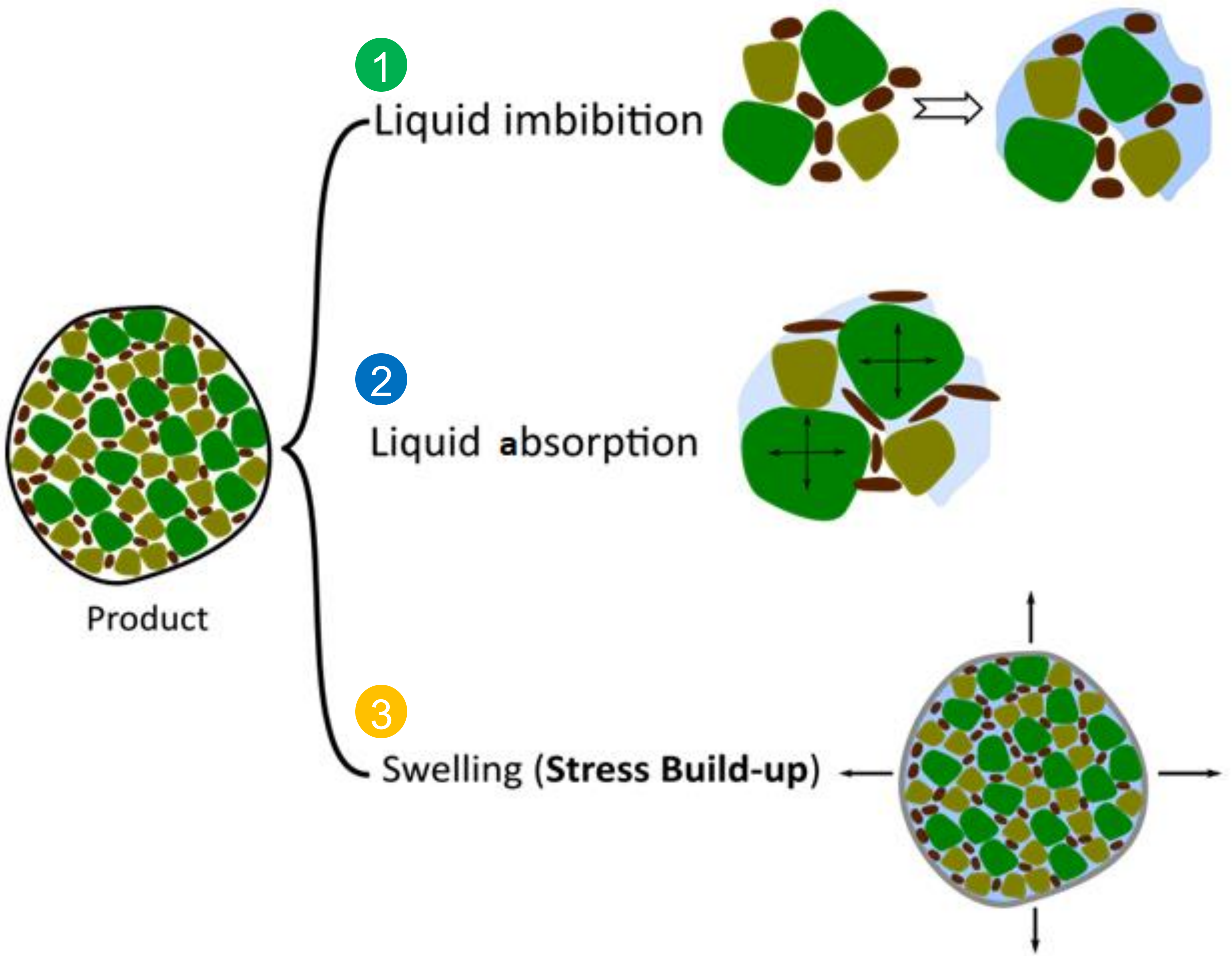
Granule Disintegration Model





Inverse Problem

Single Granule Swelling Mechanisms



1 Liquid penetration rate at granule's surface based on Darcy's law

$$\left(\frac{dV_l}{dt}\right)_{sin} = \overbrace{4\pi R^2 \frac{k_{per}}{\eta} \lim_{r\to R} \frac{\partial P_c}{\partial r}} - \underbrace{\sum n_{p,i} \frac{dV_{p,i}}{dt}}_{\text{Total liquid absorbance by the solid phase}}$$

$$V_l = \varepsilon S V$$

2

$$\left(\frac{dV_{s,i}}{dt}\right)_{sin} = n_{p,i} \frac{dV_{p,i}}{dt}$$ → liquid absorbance by i[th] component in the solid phase

$$\sum V_{s,i} = (1-\varepsilon)V = \sum n_{p,i} V_{p,i} + V_{binder}$$

3

$$\frac{\varepsilon - \varepsilon_0}{\Delta\varepsilon_\infty} = 1 - (1 - \widehat{m}_s)^\beta$$

$$\widehat{m}_s = \frac{\sum w_i Q_i^{abs} - 1}{\sum w_i Q_i^{max} - 1}$$

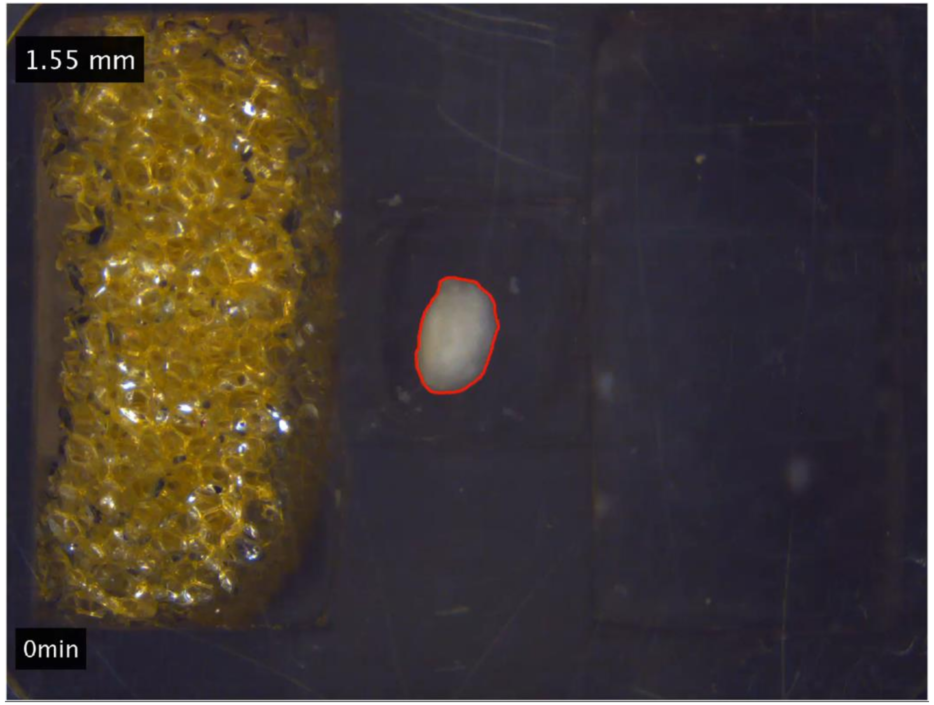
$$Q_i = \frac{\rho_l}{\rho_{s,i}} \frac{V_{p,i}}{V_{p.i}(0)} - \frac{\rho_l}{\rho_{s,i}} + 1$$

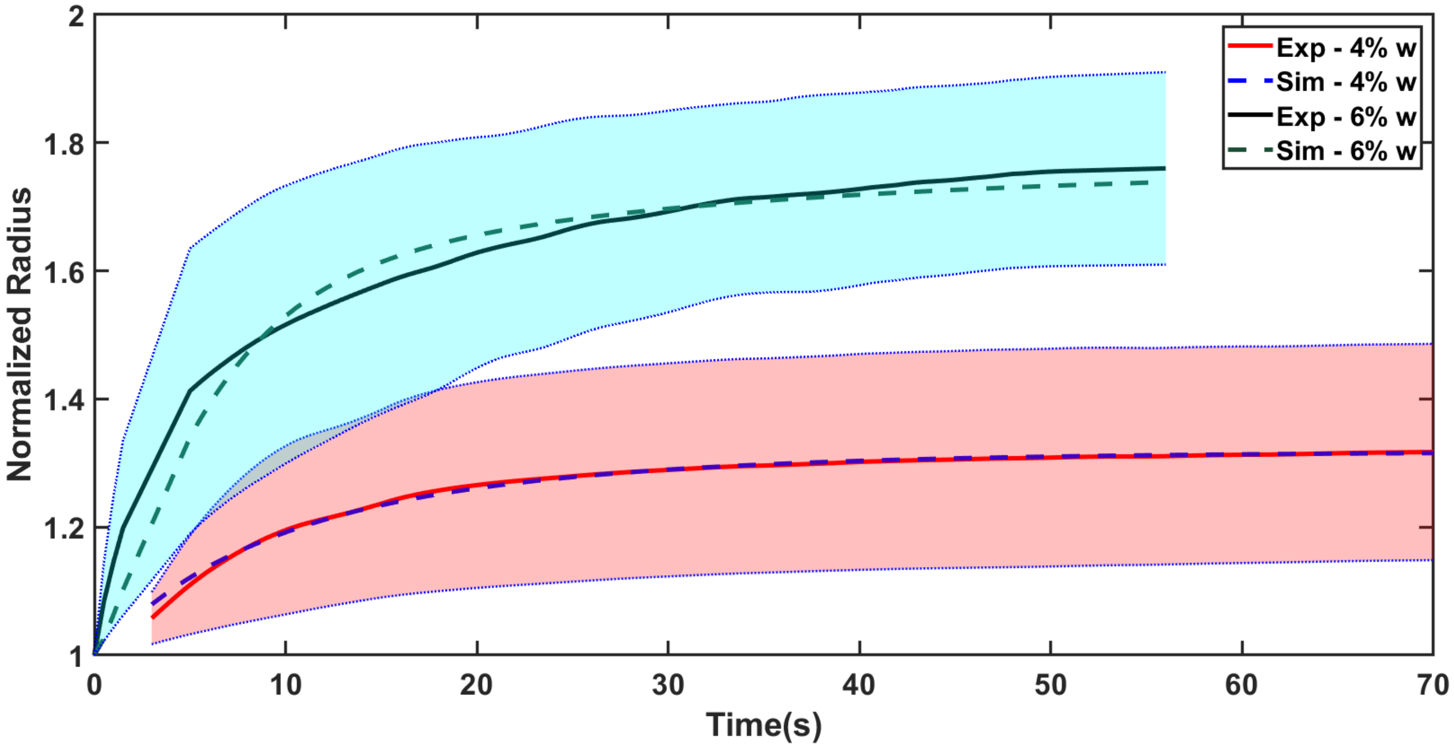
→ Dependency of porosity on mass absorption ratios of solid phase

t: time, R: granule radius, ε: porosity, S: saturation, V: volume, V_l: volume of liquid in granule, k_{per}: permeability, P_c: capillary pressure, $n_{p,i}$: number of i[th] component in the solid
$V_{p,i}$: volume of a single i[th] component particle, $V_{s,i}$: volume of i[th] component in the granule, V_{binder}: volume of the binder in the granule, $x_{v,i}$: volume fraction of i[th] component in the solid
Q_i: mass absorption of i[th] component, Γ_i: porosity factor of i[th] component, ε_0: initial porosity, $\Delta\varepsilon_\infty$: porosity difference at infinite , $\rho_{s,i}$: density of i[th] component, $\widehat{m}_s$: normalized liquid uptake
w_i: mass fraction of components, ρ_l: fluid density ,$V_{p.i}(0)$: initial volume of a single i[th] component particle

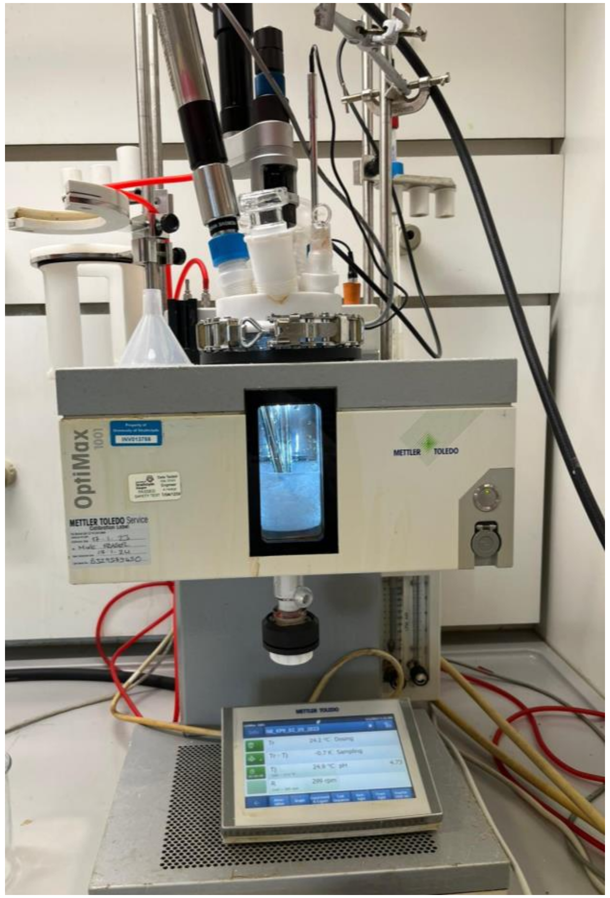
Granule swelling characterisation – flow cell

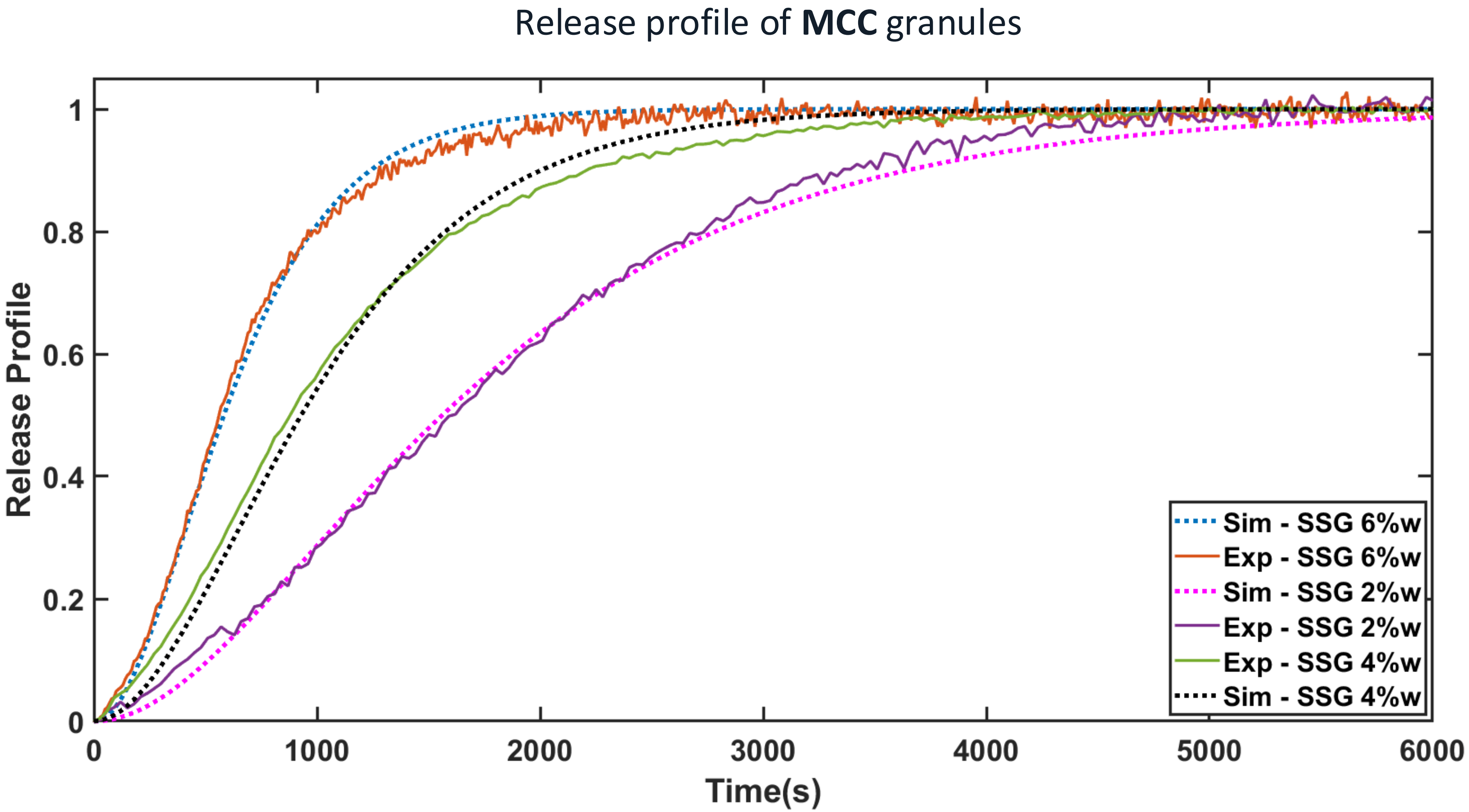
- Granule Size = 1- 1.4 mm
- SSG = 0 % , L/S =1, HPMC Conc = 12.5%



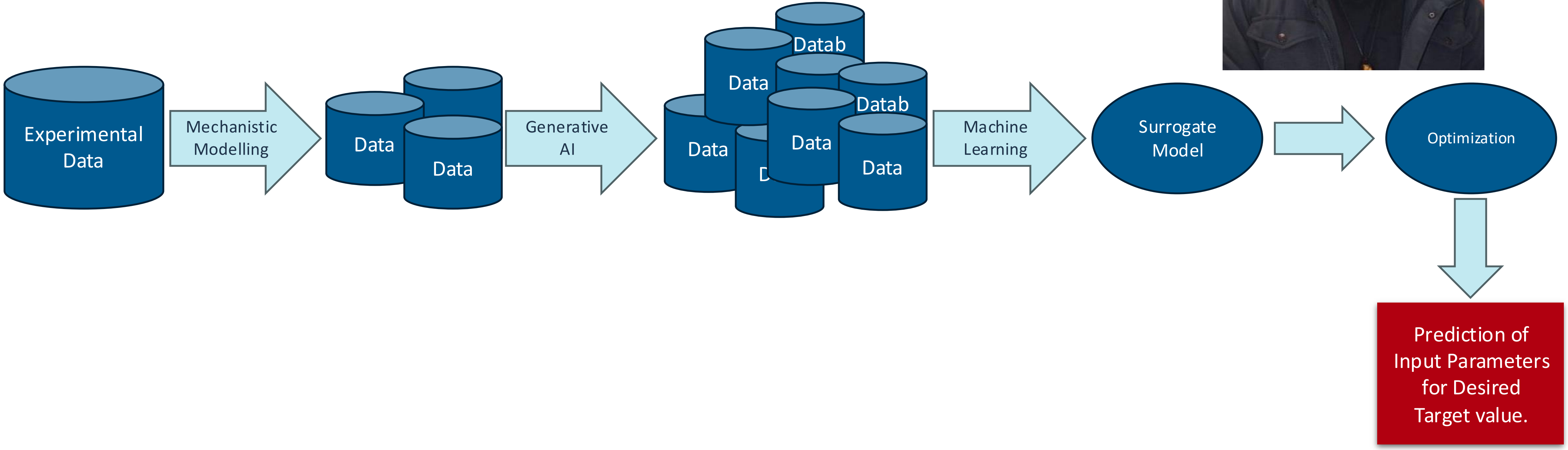


Parameter estimation and validation





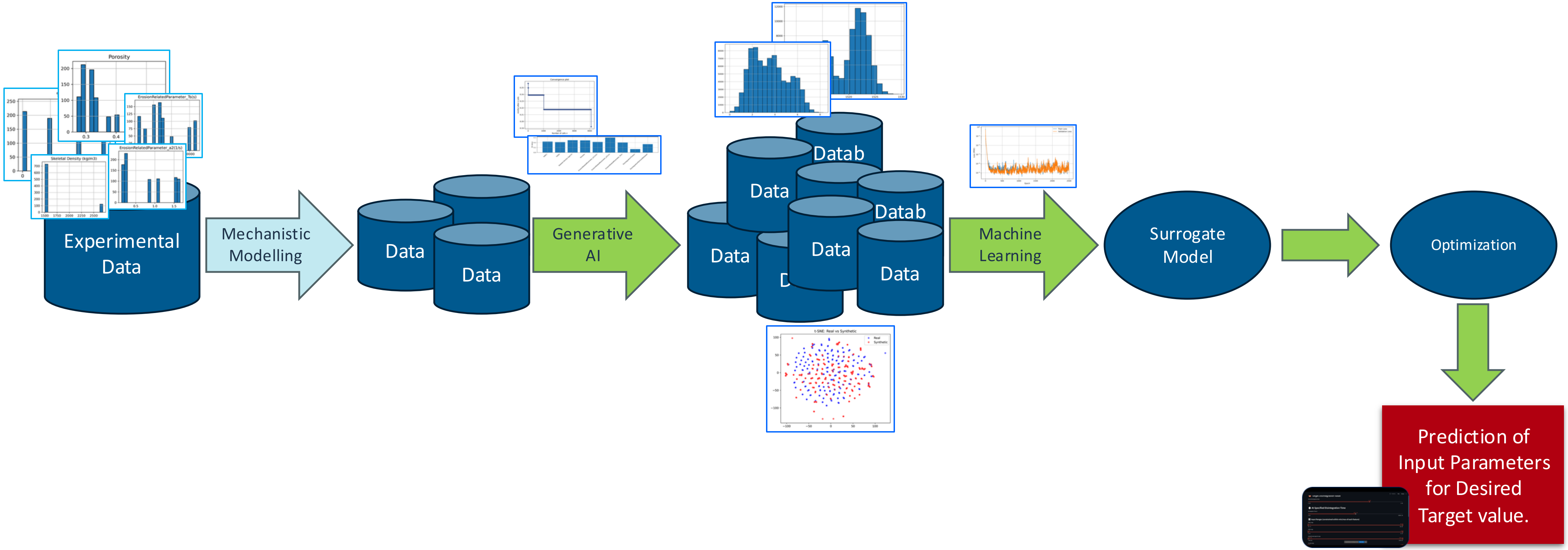
Project overview



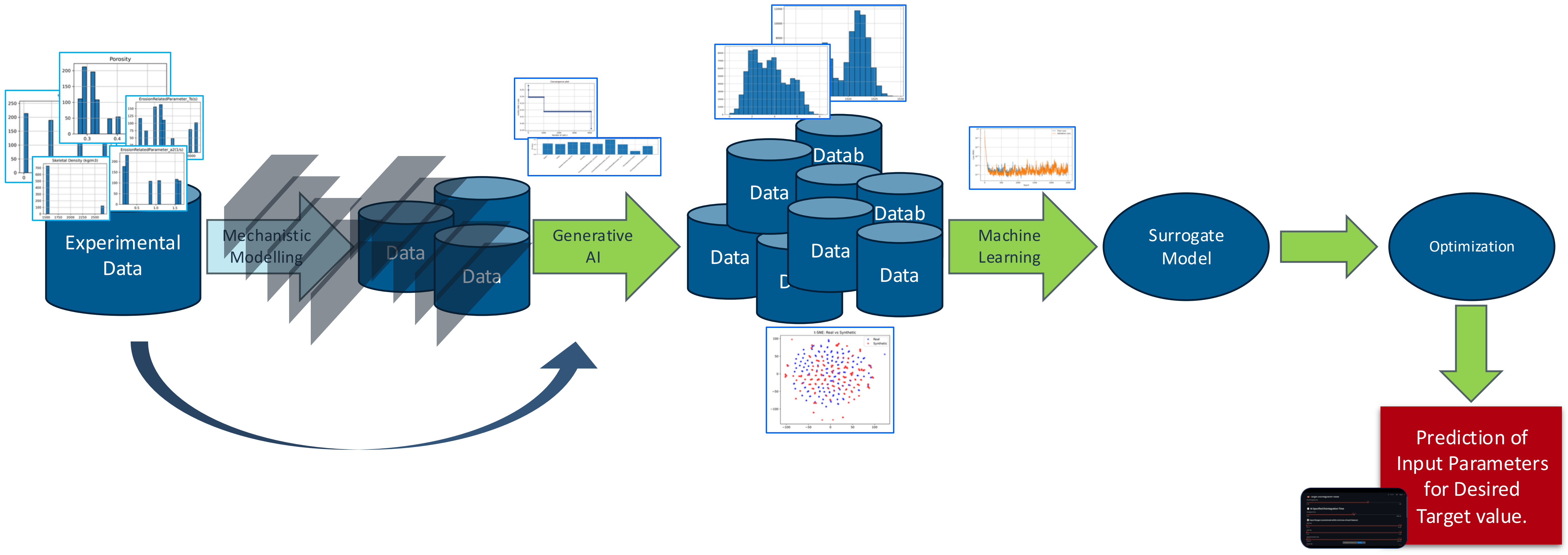
Planned Workflow

Step	Process	Mathematical Representation
1	Experimental data	$\mathcal{D}exp = \{(x_i, y_i)\}_{i=1}^{n}$
2	Mechanistic Model interpolation	$\widehat{y_{\text{mech}}} = f_{\text{mech}}(x; \phi)$
3	Generative AI to expand data	$\tilde{x} = G(z; \theta_G)$
4	ML model trained on expanded data	$\widehat{y_{\text{ML}}} = f_{\text{ML}}(x; \theta_{ML})$
5	Optimization using surrogate model	$\hat{x} = \arg\min_{x} \mathcal{L}\left(f_{\text{ML}}(x), y_{\text{target}}\right)$

Recent Progress

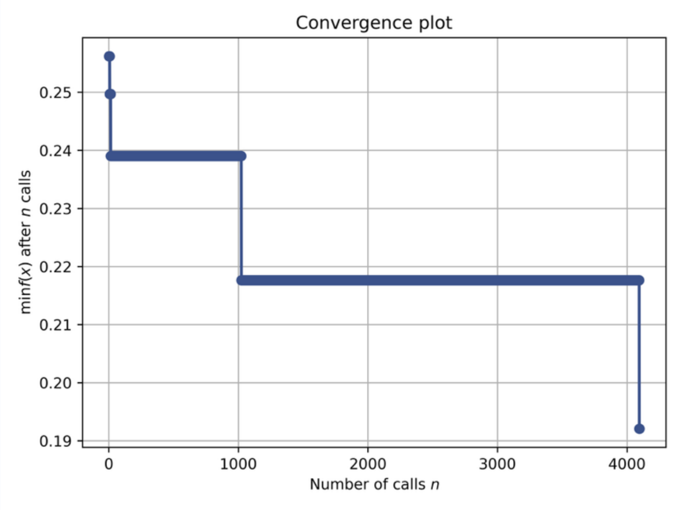


Recent Progress

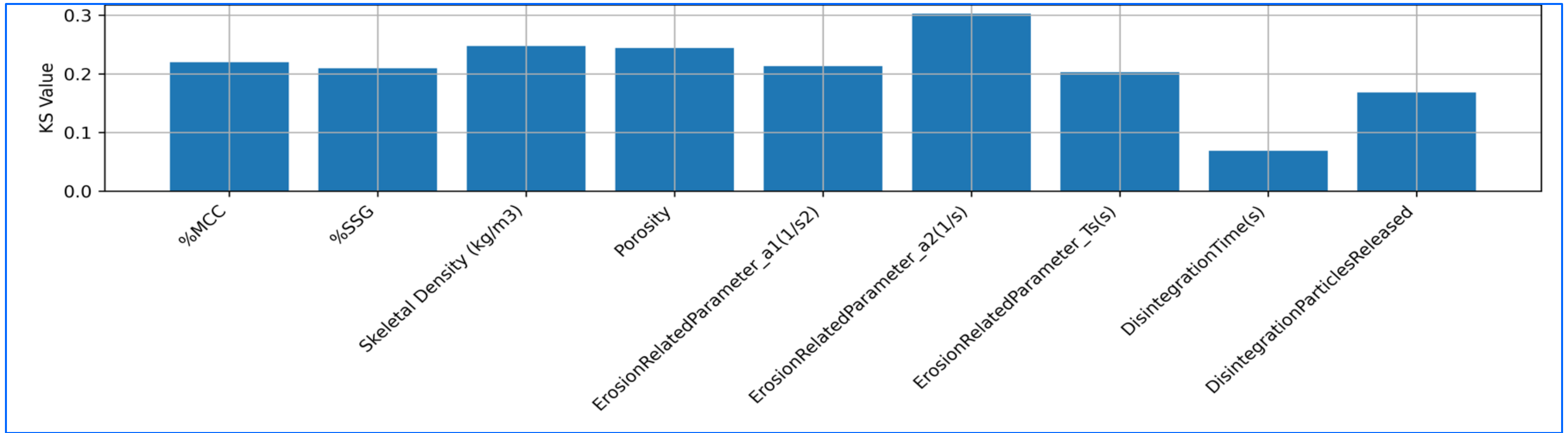


Preliminary Data Generation

- Generative Adversarial Network (GAN) have been trained for data generation.
- The Kolmogorov-Smirnov (KS) value of 0.19205 which shows moderate alignment between the real and generated data.
- To have a valid generated data, KS test must be < 0.2.



Average KS per iterations

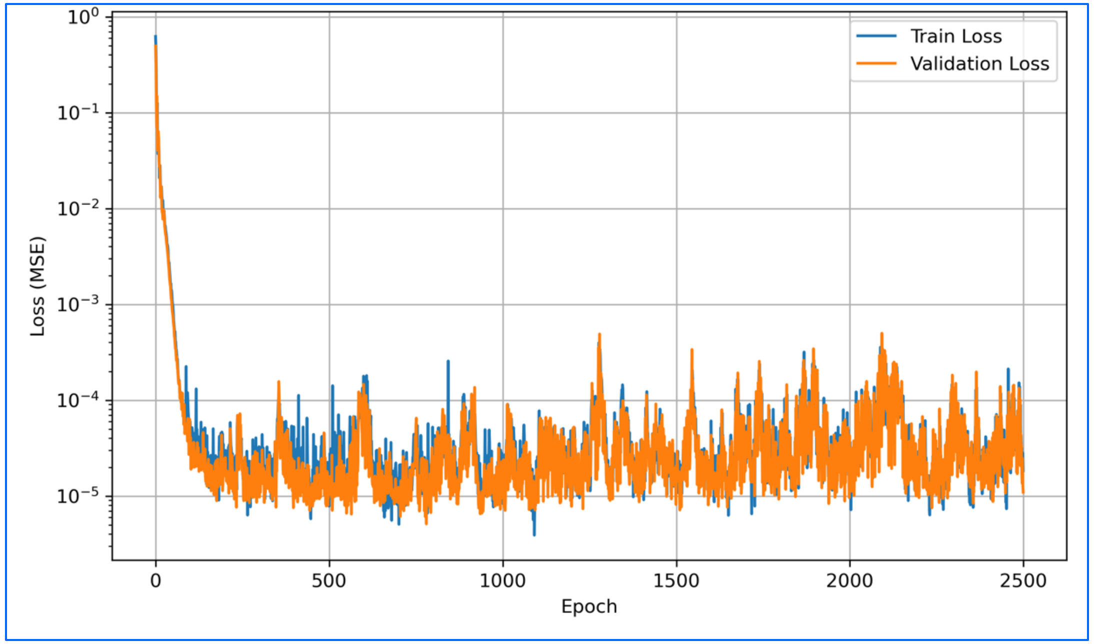


KS values per features

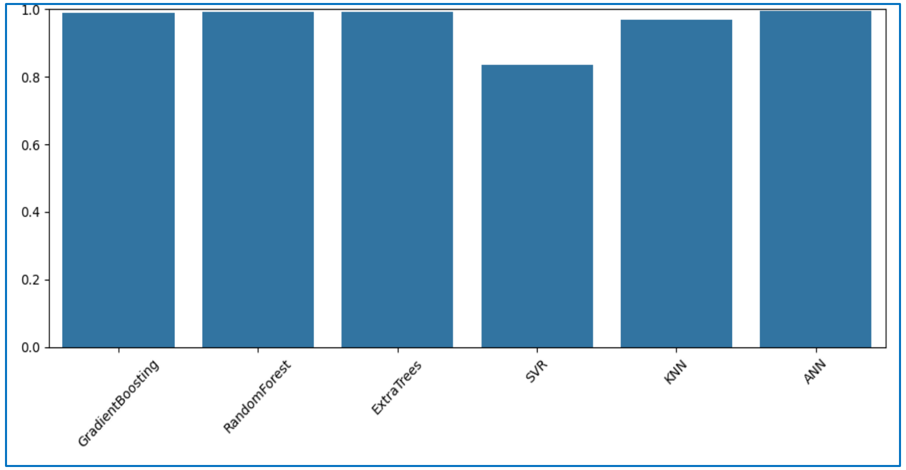
Goodfellow et al., NeurIPS 2014 — "Generative Adversarial Nets"

Training Forward Models for Predicting Disintegration profiles

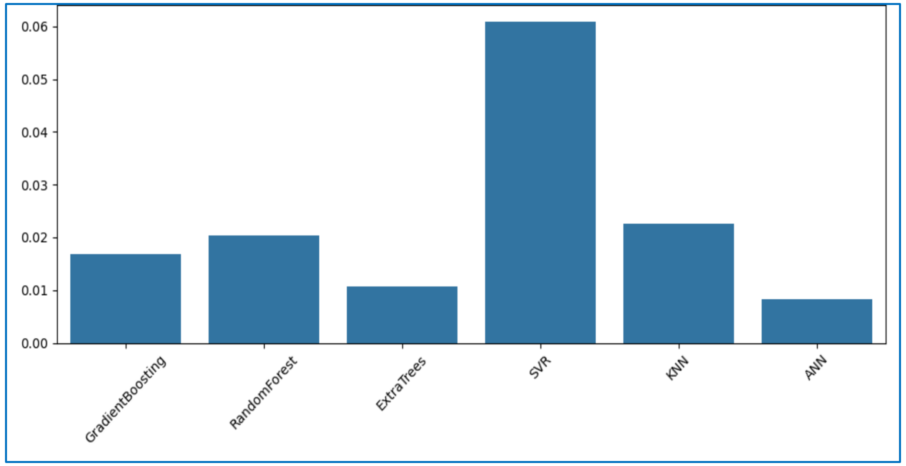
- Different ML based models have been trained to predict disintegration profile.
- Artificial Neural Network found to be the best model.
- MSE between $10^{-4} – 10^{-5}$ for validation loss of predicting disintegration value.



Train and validation loss curves for optimized ANN model



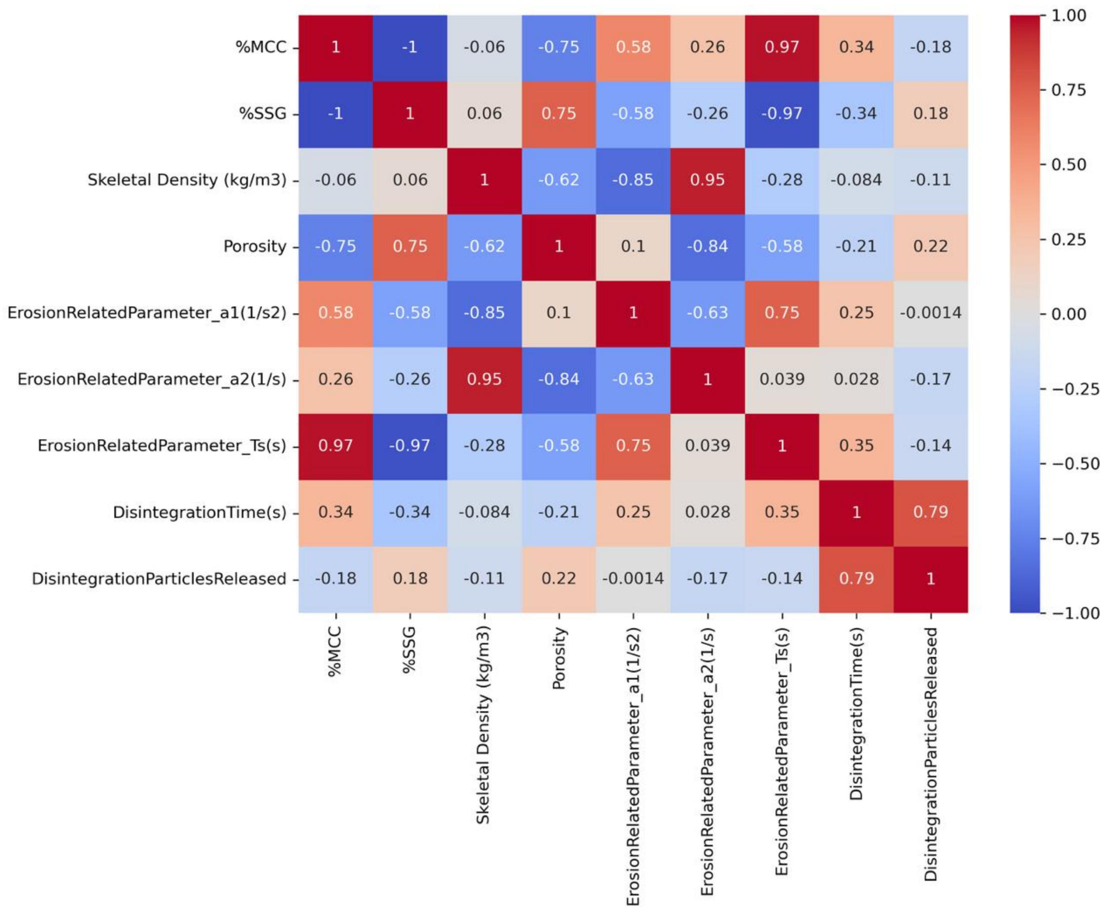
R^2 values for trained models



MSE values for trained models

Data Analysis

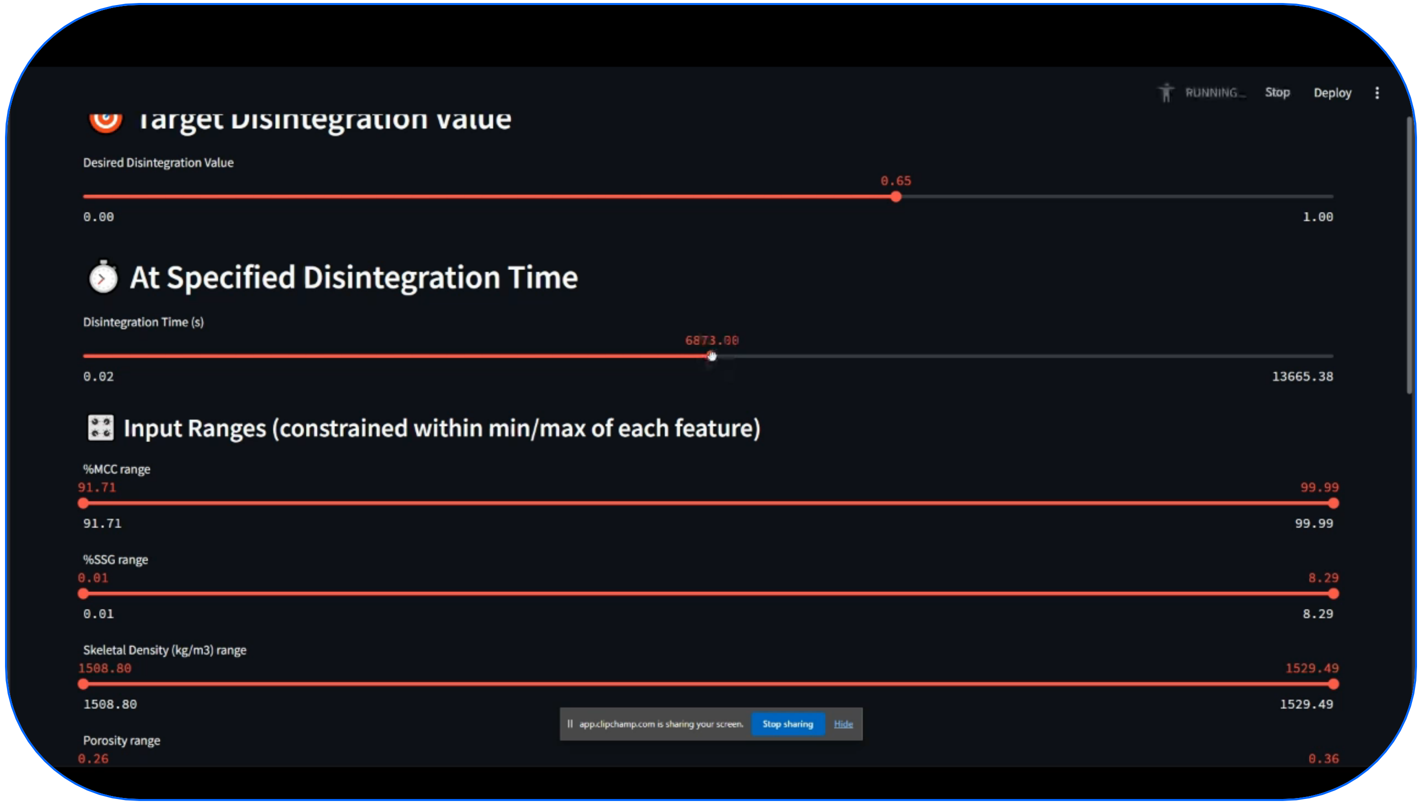
- Good correlation of disintegration value with Porosity of granules.
- Erosion Parameters (a_2(1/s), T_s(s)) are effective parameters in modelling.
- %SSG is a valuable parameter for better disintegration but less than Porosity



Correlation matrix of the properties included in the dataset

Preliminary Inverse Modelling

- Inverse Modelling is done with the generated data.
- Bayesian Optimization (global optimization) used to predict manufacturing parameters to have desired disintegration value at a specific time.
- User Interface (UI) made for practical usage.
- User can also select the accuracy threshold to get answer in case of non-realistic selection of the disintegration rate.
- Disintegration profiles is plotted for the detected granules.



Summary

- A hybrid framework combining experimental data, generative AI, and machine learning was developed for inverse formulation design.
- GAN was used to generate realistic synthetic data (e.g. porosity, skeletal density), expanding the dataset beyond original measurements.
- A trained ANN achieved high accuracy in predicting disintegration profiles, with validation MSE between 10^{-4} and 10^{-5} .
- Bayesian Optimization was integrated into a custom-built user interface to identify optimal input features that achieve user-defined disintegration targets.

Planned Further Work

- Integration of mechanistic modelling for expanding the data space.
- Improving models to get high quality data from Generative AI or mechanistic modelling.
- Using Variational Auto Encoders, as another inverse modelling approach to compare with the existing optimization method.
- Validating the inverse modelling approaches by testing the results within lab and update the approaches to reduce the potential errors of the process.
- Generalizing and including the whole processes within the UI, so that researchers from different labs could be able to use it and reduce the test and trials.

University of Sheffield

PARTICLE TECHNOLOGY GROUP

IFPRI International Fine Particle Research Institute

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