Factorial Data-Driven Inverse Design of Granular Hydrogels for Targeted Therapeutic Release

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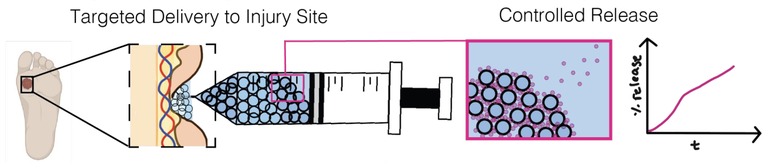
Introduction

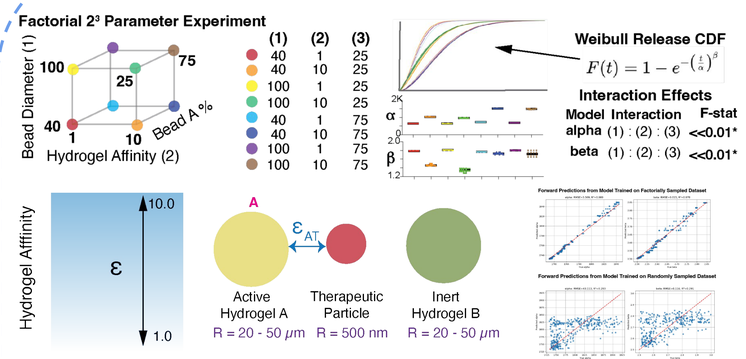
Granular hydrogel scaffolds, composed of functionalized, packed polymer microgels, achieve **targeted and sustained release**. They can be loaded with therapeutics, like **drug-coated nanoparticles** or **extracellular vesicles**, and injected directly into the target site. The transport dynamics of the therapeutic particles can be tuned by the scaffolds':

- **porosity (size of microgels)**
- **surface chemistries (hydrogel-therapeutic interaction strength, and**
- **heterogeneity (microgel mixtures with different interaction potentials).**



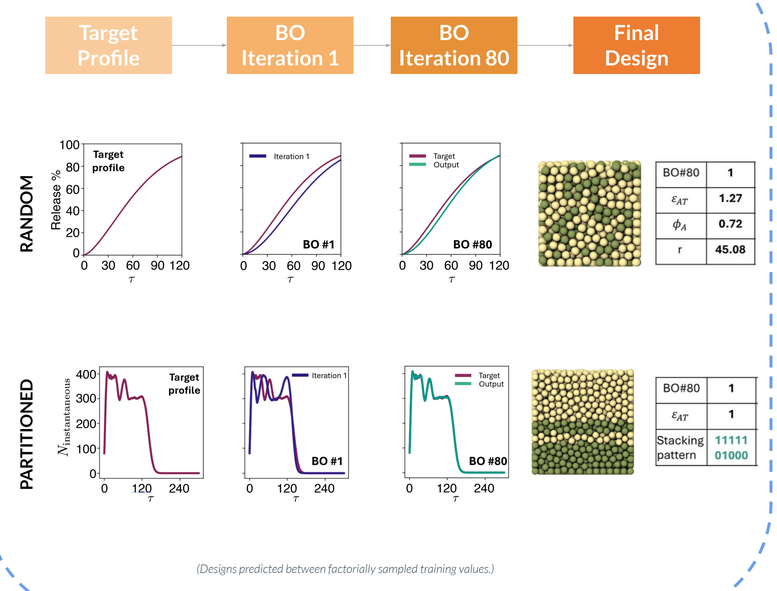
This feature set expands the design space of this material, making it highly modular but also intractable from a data analysis and experimentation standpoint. Here, we present a programmable therapeutic release simulation for this material platform. Using factorial experimental design, we identify a practical design space that supports precision medicine through ML-driven **inverse design of programmable drug release profiles**, including tunable cumulative release profiles through random packing and instantaneous release profiles through layered packing.

Parameterization by Factorial DOE



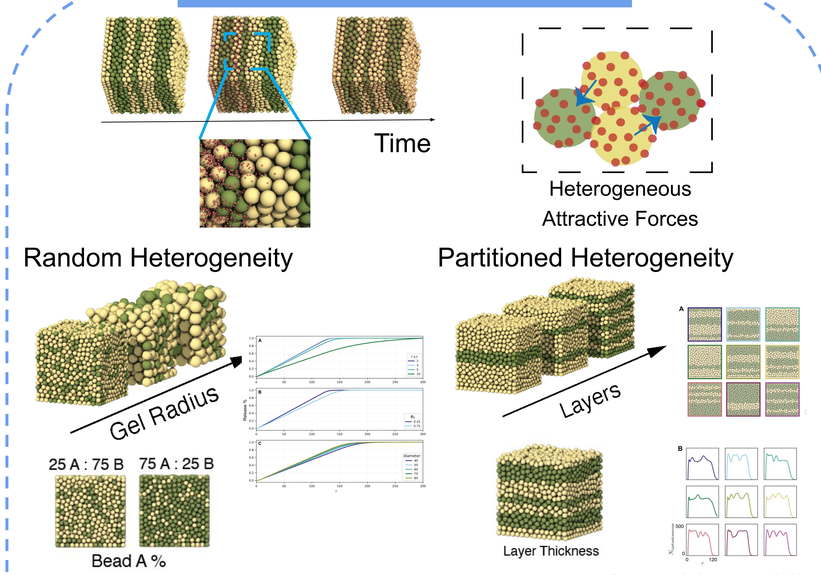
We bound our design space by evaluating highs and lows of each simulation parameter with a simple 2-level, 3-factor(2^3) factorial design of experiment. Thus, we start by analyzing only 8 simulation configurations. We verify that the design space bounded within the DOE cube exhibits meaningful interaction effects on the therapeutic particles' cumulative release profile (modelled as a Weibull release cumulative distribution function). We also observe that training models on factorially sampled vs randomly sampled data leads to better generalization.

Targeted Release Kinetics by Design



(Designs predicted between factorially sampled training values.)

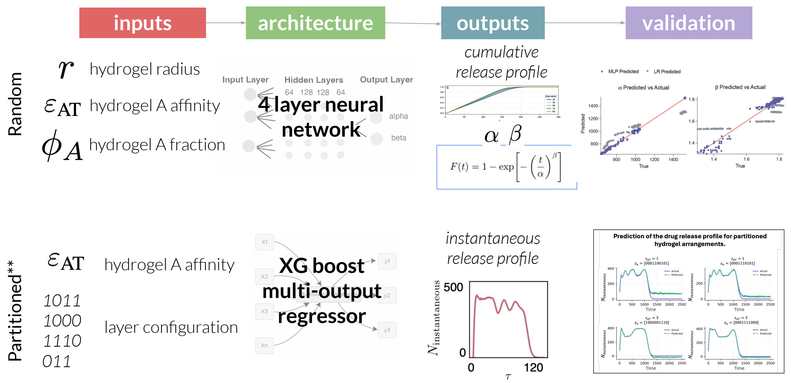
Simulation Design Space



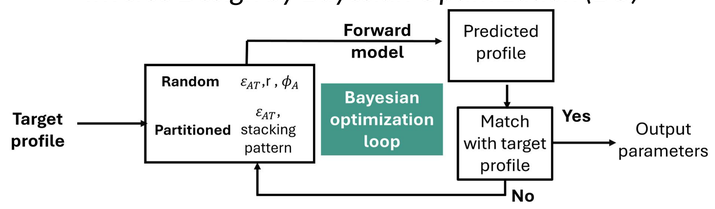
We developed a **coarse-grained model** for granular hydrogels (yellow (A), green (B)) loaded with therapeutic particles (red) and studied the transport behavior using **molecular dynamics (MD)** simulation. The two hydrogel types, A and B, indicate **heterogeneous interaction potentials** with the therapeutic. Two overarching configurations were extensively explored: **random mixtures** of A and B; and **partitioned layers** of A and B.

Inverse Design Approach

Forward Models



Inverse Design by Bayesian Optimization (BO)



** Partitioned model was only trained for gel radius systems of 40 μm

Conclusions & Next Steps

We developed a **simulation-forward inverse design framework** capable of accurately predicting granular hydrogel scaffold designs that yield diverse therapeutic release profiles across both cumulative and instantaneous time scales. This approach represents a critical advancement toward **precision medicine** by automating design generation, enhancing predictive accuracy, and substantially reducing experimental costs associated with optimizing controlled release systems. **We plan to incorporate experimental data in future work.**

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