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

Yasha Saxena*[1], Po-An Lin*[2], Jay Shah*[3], Tracy Asamoah[4], Arthi Jayaraman[3], Gaurav Arya[2], and Tatiana Segura[1]

[1]Department of Biomedical Engineering, Duke University
[2]Department of Mechanical Engineering and Materials Science, Duke University
[3]Departments of Chemical and Biomolecular Engineering and Materials Science and Engineering, University of Delaware
[4]Pritzker School of Molecular Engineering, University of Chicago

Abstract

Grandular hydrogels enmeshed with therapeutic particles offer an exciting modular platform for the delivery of targeted therapeutics, but this modularity also complicates the optimization of the design. Here, we present a programmable therapeutic release simulation for this material platform. Using factorial experimental design, We efficiently validate simulation parameters and identify a practical design space that supports precision medicine through the inverse design of unique and customizable drug release profiles, including tunable cumulative release profiles through random packing and tunable instantaneous release profiles through layered packing.

1 Introduction

Granular hydrogel scaffolds, composed of packed polymer microgels, achieve targeted and sustained release, making them exciting platforms for precision medicine. They can be loaded with therapeutics, like drug-coated nanoparticles or extracellular vesicles, and injected directly into the target site (Figure 1). The transport dynamics of the scaffold can be tuned by its porosity, surface chemistry, and heterogeneity [1–4].

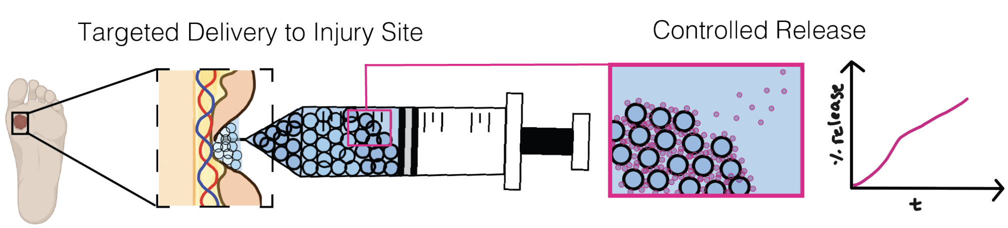

Figure 1: Granular Hydrogel Therapeutic Delivery Achieves Targeted and Controlled Delivery

While the modularity of the material is a key advantage, it also creates a high-dimensional design space that is challenging to navigate both experimentally and computationally. Inverse design models have recently emerged to map desired material behaviors back to feasible designs. However, they

*Equal contribution.

31st AI4Mat-NeurIPS (NIPS 2025), San Diego, CA, USA.

typically require large and diverse datasets to adequately capture the complexity of the design space [5, 6]. Moreover, the inverse design problem is often ill-posed: multiple design configurations may yield similar material properties, the design–property landscape may be non-smooth, or some desired properties may have no feasible design solution [7–9]. Generating sufficiently rich datasets experimentally is demanding, so simulation-forward approaches are often used to generate data and guide experiments. Several simulation works have been performed to study the transport phenomena in hydrogel systems and porous media. Most notably, computational fluid dynamics (CFD) and rigid-body simulations have been employed to capture transport properties such as permeability, flow paths, and tortuosity[10–12]. However, moelcular-scale events, such as surface diffusion on hydrogel beads, Knudsen-like diffusion (inter-scaffold hopping), and jamming, that are important to the drug release profile are difficult to capture with CFD [13]. Molecular dynamics (MD) simulations, by contrast, provide a versatile framework to model these molecular transport phenomena with higher fidelity[14–17].

In this work, we developed a coarse-grained model for granular hydrogels loaded with therapeutic particles, studied the transport behavior using MD simulation, and developed an inverse design pipeline to identify several target profiles with high precision. This approach accelerates discovery of statistically relevant relationships in the design space, while substantially reducing the computational overhead of an exploratory data analysis on a more random and continuous sampling of the space. Our main contributions are: (1) a simulation-forward platform for discovering new release kinetics in multidimensional therapeutic hydrogel scaffolds, (2) implementation of a statistics-driven methodology for computationally efficient design space discovery, and (3) an effective inverse design platform for customizing release kinetics with generated scaffold designs.

2 Results and Discussion

2.1 Data Preparation and Design Space

Transport in granular hydrogel scaffolds is influenced by several factors, including system porosity, interaction strength between the gel and the transported particle, and the heterogeneity of surface chemistries, all of which define our design space[18]. To efficiently explore this space, a two-level, three-factor factorial design was implemented to identify key regions of interest. Simulations were run for eight combinations of hydrogel A affinity (ε_{AT}), bead diameter (r), and hydrogel A fraction (ϕ_A) (Figure 2A). Scaffold geometries were generated by randomly packing monodisperse rigid spheres into a fixed cubic volume. The scaffolds comprised two hydrogel types: A and B(Supplemental 1.1.1-1.1.2). Release kinetics of the therapeutic particle T were characterized by fitting cumulative release curves to the α and β parameters of a Weibull distribution (Supplemental 1.1.3). The selected combinations (Figure 2A) showed significant interaction effects on the α and β terms, indicating that design combinations of these parameters would yield interesting variation on release kinetics (Supplemental 1.2.4). Thus, we move forward with combinations within this design space (Figure 2B). From this space, two overarching configurations are extensively explored for inverse design: (1) random mixtures of A and B and (2) partitioned layers of A and B (Figure 2C).

2.2 Inverse Design

We implemented an inverse design framework to identify multiple sets of hydrogel design parameters that achieve distinct desired release profiles in parallel. For random mixture designs, the input design parameters are $\boldsymbol{\theta} = [r, \varepsilon_{\text{AT}}, \phi_A]$; for partitioned designs, the input design parameters are ε_{AT} and a binary array representing layer configuration (Supplemental 1.1.1). Various Weibull release profiles achieved by random mixture designs are shown in Figure 2A and Supplemental Figure 3, while the diverse instantaneous release profiles achieved by partitioned designs are shown in Figure 3.

The forward models are tasked to predict the resulting release profile (cumulative for random, instantaneous for partitioned) given the input design parameters. The dataset was divided into training, validation, and held-out testing sets in a 70/10/20% split. To create target profiles, we randomly selected six profiles from our held-out test dataset. The difference between the predicted and target profiles is evaluated using a mean-squared error (MSE) loss function, and Bayesian optimization (BO) iteratively proposes new parameter sets to minimize this difference. This adaptive, inverse-design loop efficiently converges to parameter combinations that match the target profile by interacting with the (surrogate) forward model, enabling rapid exploration of the design space without

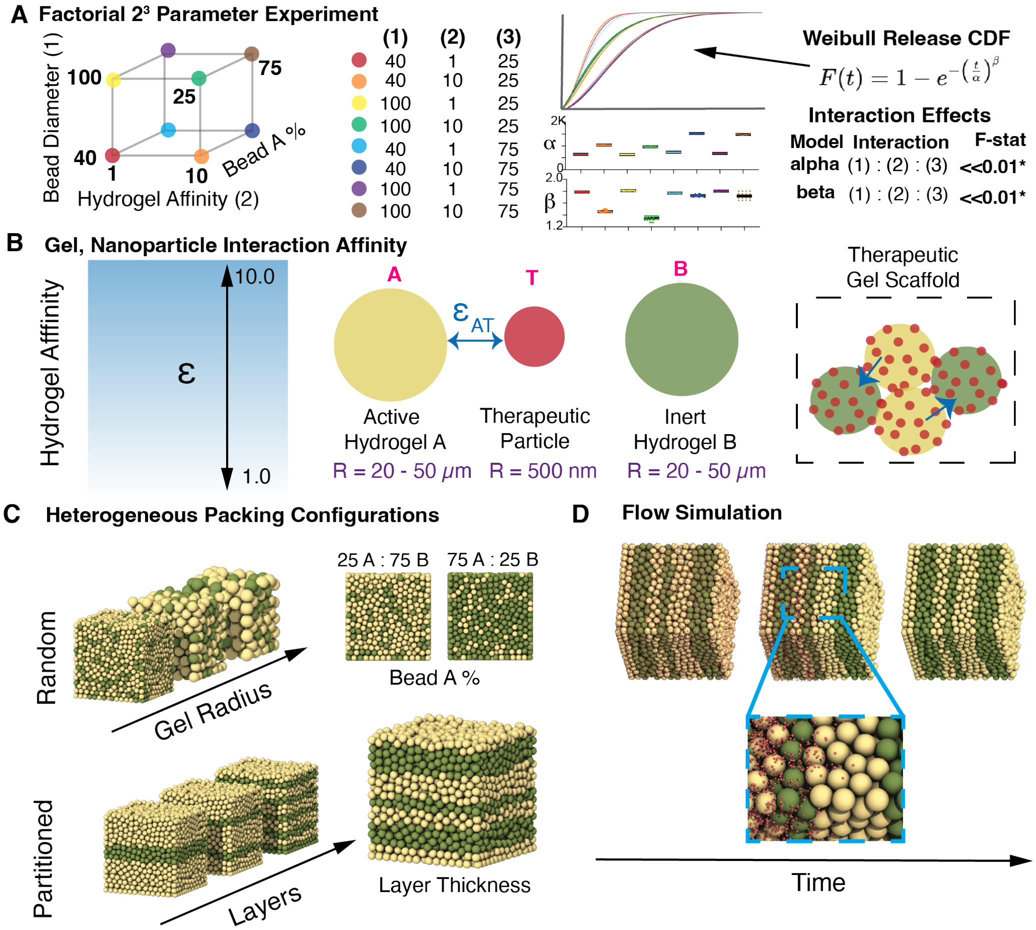

Figure 2: Factorial Data Driven Design Space of Coated Granular Hydrogel Scaffolds

repeated costly MD simulations, and is applicable to both cumulative release in random geometries and instantaneous release in partitioned geometries (Supplemental 1.2).

2.2.1 Random Mixtures

We trained a three-layer neural networks to predict α and β from the input parameters $\boldsymbol{\theta} = [r, \varepsilon_{AT}, \phi_A] \in \mathbb{R}^3$ (Supplemental Methods 1.1.6). This simple, lightweight neural network outperforms linear regression (Supplemental Figure 1). Inspired by the initial factorial experiment, models were trained on a factorially sampled dataset (Supplemental Table 3), which outperformed models trained on randomly sampled data set (Supplemental Table 4). This aligned with previous observations that factorial sampling provides more systematic coverage of the parameter space than random sampling when data is scarce[19]. Data scarcity is often the case with wet-lab experiments. We apply the inverse design framework to the forward model trained on the factorially sampled data and within 80 iterations of BO, we successfully obtain release profiles close to the target profiles 4.

2.2.2 Partitioned Mixtures

Next, we explore partitioned designs that enable greater temporal control over instantaneous drug release than random mixture design. With the insights we gained from random mixture design, we focus on diameter 40 μm and create a partitioned system where Hydrogel A and B are layered at varying partition widths (Supplemental 1.1.1). Here, we used XGboost as our surrogate forward model, which enables accurate prediction on instantaneous release profiles from design inputs (Supplemental 1.1.6, Supplemental Figure 4). Again, the inverse design framework is able to recover the target designs. Notably, in some cases, the tail behaviors are difficult to predict accurately (Supplemental Figure 4). We aim to address this in the future by incorporating more data and increasing data diversity.

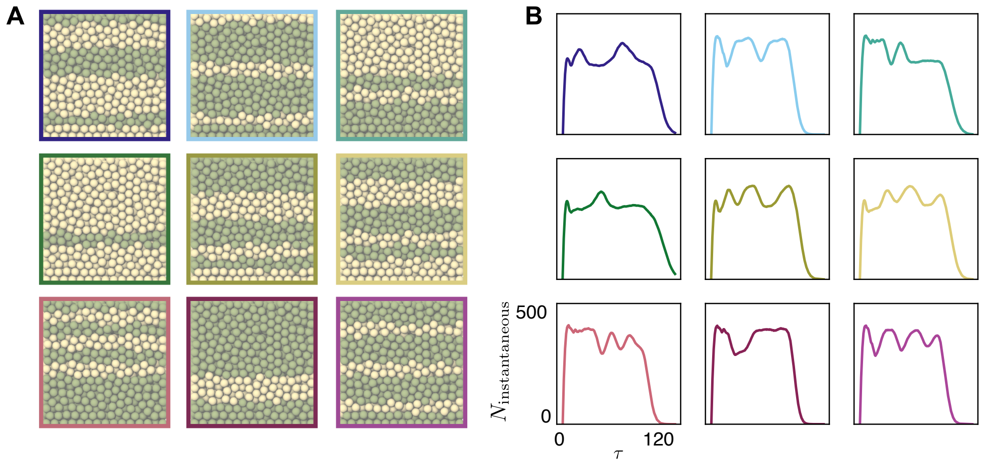

Figure 3: Programmable drug release profiles with partitioned geometries. (A) Side views of nine selected partitioned designs, and (B) their corresponding instantaneous release profiles with respect to time τ.

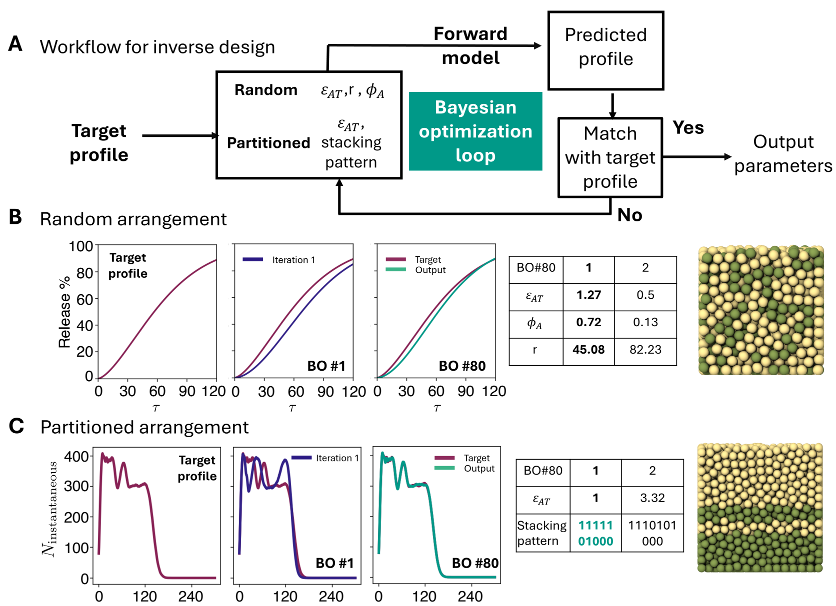

Figure 4: Inverse design on drug release profile. (A) Inverse design workflow. Inverse design on (B) random and (C) partitioned hydrogel arrangements

3 Conclusion

We developed a data-efficient, simulation-forward inverse design framework capable of accurately predicting granular hydrogel scaffold properties 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.

4 References

[1] Andrew C Daly, Lindsay Riley, Tatiana Segura, and Jason A Burdick. Hydrogel microparticles for biomedical applications. *Nature Reviews Materials*, 5(1):20–43, 2020.

[2] Shuhan Feng, Kaiyang Chen, and Shiqi Wang. Practical guide to the design of granular hydrogels for customizing complex cellular microenvironments. *Advanced Healthcare Materials*, page e01947, 2025.

[3] Jianyu Li and David J Mooney. Designing hydrogels for controlled drug delivery. *Nature Reviews Materials*, 1(12):1–17, 2016.

[4] Alexa R Anderson, Ethan Nicklow, and Tatiana Segura. Particle fraction is a bioactive cue in granular scaffolds. *Acta biomaterialia*, 150:111–127, 2022.

[5] Benjamin Sanchez-Lengeling and Alán Aspuru-Guzik. Inverse molecular design using machine learning: Generative models for matter engineering. *Science*, 361(6400):360–365, 2018.

[6] Yongtao Liu, Tian Zhao, Wen Ju, and Siqi Shi. Materials discovery and design using machine learning. *Journal of Materiomics*, 7(3):593–605, 2021.

[7] Po-An Lin, Simiao Ren, Jonathan Caswell Piland, Leslie M Collins, Stefan Zauscher, Yonggang Ke, and Gaurav Arya. Deep inverse design of hydrophobic patches on dna origami for mesoscale assembly of superlattices. In *AI for Accelerated Materials Design-NeurIPS 2023 Workshop*.

[8] Simiao Ren, Willie Padilla, and Jordan Malof. Benchmarking deep inverse models over time, and the neural-adjoint method. *Advances in neural information processing systems*, 33:38–48, 2020.

[9] Simiao Ren, Ashwin Mahendra, Omar Khatib, Yang Deng, Willie J Padilla, and Jordan M Malof. Inverse deep learning methods and benchmarks for artificial electromagnetic material design. *Nanoscale*, 14(10):3958–3969, 2022.

[10] Agnese Marcato, Gianluca Boccardo, and Daniele Marchisio. From computational fluid dynamics to structure interpretation via neural networks: An application to flow and transport in porous media. *Industrial & Engineering Chemistry Research*, 61(24):8530–8541, 2022. doi: 10.1021/acs.iecr.1c04760.

[11] Teoh Jia Heng, Abdul Shakoor Faheemah Tasneem, and Wang Chi-Hwa. 3d printing methyl cellulose hydrogel wound dressings with parameter exploration via computational fluid dynamics simulation. *Pharmaceutical Research*, 39(2):281–294, 2022.

[12] Shuai Li, Yuanyuan Liu, Yu Li, Yanan Zhang, and Qingxi Hu. Computational and experimental investigations of the mechanisms used by coaxial fluids to fabricate hollow hydrogel fibers. *Chemical Engineering and Processing: Process Intensification*, 95:98–104, 2015.

[13] Alexander Schlaich, Jean-Louis Barrat, and Benoit Coasne. Theory and modeling of transport for simple fluids in nanoporous materials: From microscopic to coarse-grained descriptions. *Chemical Reviews*, 125(5):2561–2624, 2025. doi: 10.1021/acs.chemrev.4c00406.

[14] M BRAZIL. Molecular dynamic study of fluid flow through porous medium. *Brazilian Journal of Physics*, 25(4), 1995.

[15] Ulrich Tallarek, Dzmitry Hlushkou, and Alexandra Höltzel. Solute sorption, diffusion, and advection in macro–mesoporous materials: Toward a realistic bottom-up simulation strategy. *The Journal of Physical Chemistry C*, 126(5):2336–2348, 2022. doi: 10.1021/acs.jpcc.1c10137.

[16] Colin Bousige, Pierre Levitz, and Benoit Coasne. Bridging scales in disordered porous media by mapping molecular dynamics onto intermittent brownian motion. *Nature Communications*, 12(1):1043, 2021.

[17] Hossein Salahshoor and Nima Rahbar. Multi-scale mechanical and transport properties of a hydrogel. *Journal of the mechanical behavior of biomedical materials*, 37:299–306, 2014.

[18] Rui-Chian Tang, Lily Shang, Philip O Scumpia, and Dino Di Carlo. Injectable microporous annealed crescent-shaped (mac) particle hydrogel scaffold for enhanced cell infiltration. *Advanced Healthcare Materials*, 13(25):2302477, 2024.

[19] Turab Lookman, Prasanna V Balachandran, Dezhen Xue, and Ruihao Yuan. Active learning in materials science with emphasis on adaptive sampling using uncertainties for targeted design. *npj Computational Materials*, 5(1):21, 2019.