

Title: Machine Learning-Based Design of a 3D-Printable Bioink for Neural Tissue Engineering Using Stem Cell-Derived Neural Progenitor Cells

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Introduction: 3D bioprinting presents a promising avenue for creating biomimetic tissues with applications in regenerative medicine and disease modeling. However, the development of ideal bioinks remains challenging due to a predominant reliance on trial-and-error approaches. As cells are highly responsive to the mechanical properties of their environment—a phenomenon governed by mechanosensing and mechanotransduction—this study hypothesizes that tuning the mechanical properties of biocompatible bioinks can enable the prediction and optimization of cellular behavior, including viability, proliferation, and functionality [1, 2].

Methods: A bioink library was formulated by varying concentrations of fibrin and alginate to achieve a wide range of mechanical characteristics. Each formulation was assessed for stiffness, viscosity, storage modulus, loss modulus, printability, swelling behavior, and degradation rate. Neural progenitor cell (NPC) viability was quantified via LDH assays at Day 1 (D1), Day 7 (D7), and Day 15 (D15). Proliferation was measured by PicoGreen assays, and functionality was evaluated through membrane depolarization using voltage-sensitive dyes. To correlate mechanical properties with biological outcomes, both traditional (Multiple Linear Regression - MLR) and machine learning (Lasso, Ridge, Elastic Net, and Support Vector Regression—SVR) models were developed.

Results: Tuning bioink formulations generated a broad distribution of mechanical properties, with no clear visual correlation to printability. Increased stiffness correlated with reduced degradation rates and elevated swelling behavior. Biologically, the formulations produced a wide range of outcomes, including both favorable and unfavorable effects on viability and proliferation. Among all models, SVR demonstrated superior predictive accuracy, particularly under conditions of limited data or nonlinear relationships. Critically, the model's performance was validated using an independent and diversified dataset comprising bioinks from plant-based, animal-derived, and synthetic sources. The SVR model maintained robust predictive capabilities across these varied compositions, indicating its strong generalizability and potential for broader application in bioink development.

Discussion: These findings confirm that mechanical properties serve as reliable predictors of cellular behavior in 3D bioprinted constructs. The lack of association between visual printability and performance reinforces the need for quantifiable, data-driven parameters in bioink design. SVR's ability to manage small datasets and minimize the impact of outliers makes it particularly well-suited for biological applications where data variability is common. The successful cross-validation using distinct bioink types further underscores the model's adaptability and translational relevance.

Conclusion: Bioink design can be significantly enhanced through the use of machine learning models that integrate mechanical properties as predictive inputs. This approach shifts development from empirical testing to informed prediction, improving reproducibility and accelerating optimization. Future work will focus on expanding model validation to additional cell types and integrating chemical property analyses to further refine predictive power and applicability across diverse tissue engineering applications.

References:

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