Machine Learning–Driven Design and Experimental Validation of Peptide-Based Mixed- Metal Organic Frameworks (MOFs) for Predictive Membrane Disruption in Targeted Immunotherapeutic Applications

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Metal-organic frameworks (MOFs) are highly tunable nanomaterials with potential in targeted immunotherapy and biological interfaces; however, the vast number of possible metal frameworks limits experimental screening. This study establishes a closed-loop, AI-guided design pipeline to model relationships between structural, electronic, and biofunctional properties of peptide-derived mixed-metal MOFs to predict membrane-disruptive behavior. Peptide-based tetracarboxylate ligands were synthesized and coordinated with $Zn^{2?}$, $Cu^{2?}$, and $Ni^{2?}$ nodes to generate hybrid frameworks under controlled stoichiometric conditions. Multimodal descriptors capturing ligand topology, hydrophobicity, charge distribution, metal ionic properties, and estimated pore dimensions were combined with experimental calcein leakage kinetics from phospholipid liposomes. A gradient boosting regression model trained with a 70/30 train–test split and 5-fold cross-validation achieved $R^2 = 0.81$ and mean absolute error <10%. Feature attribution showed ligand hydrophobicity, aromaticity, and metal ionic radius were dominant predictors, suggesting membrane disruption arises from combined chemical and electrostatic effects. $Cu^{2?}$ MOFs with hydrophobic linkers produced the highest leakage (up to 72%), while highly crystalline frameworks showed lower metal ion release and reduced biological activity, indicating a tradeoff between structural stability and membrane interaction. Experimental results were within 9% of predicted values, demonstrating the model could generalize to new MOF compositions. These findings show how integrating AI-guided computation with experimental validation accelerates targeted synthesis and enables predictive control of nanomaterial biointerfaces.

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