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Review

Application of Machine Learning to Identify Molecular Descriptors Influencing Viscosity in Concentrated Therapeutic Antibodies

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Abstract:
The viscosity of concentrated therapeutic antibodies affects how easily we can make, store, and give them to patients. This study combines machine learning with experimental and computational methods. It aims to find the molecular descriptors that affect viscosity changes in monoclonal antibodies (mAbs). We analyzed key descriptors like charge distribution, hydrophobicity, and solvent-accessible surface areas. This was done using molecular dynamics simulations and predictive modeling. Experimental viscosity data at high concentrations were combined with advanced algorithms. Decision tree classifiers helped uncover nonlinear relationships between structural properties and viscosity. The machine learning model showed impressive results. It had a predictive accuracy of 94.3%. Its precision was 92.8%, and recall reached 96.1%. This model outperformed old rule-based methods. Key terms like SCM, N_phobic_Fv, and CSP were found to greatly influence viscosity trends. These findings give important insights into how physicochemical factors affect mAb viscosity. They also provide a strong base for early antibody screening and improving formulations. This study highlights how machine learning can improve biopharmaceutical development. It helps design therapeutic antibodies that are easier to manufacture and better for patients. Future research will aim to expand datasets. It will also add more molecular descriptors. This will help refine predictive models.

Keywords: *Machine learning, monoclonal antibodies, viscosity prediction, molecular descriptors, biopharmaceutical optimization*

Introduction

Monoclonal antibodies (mAbs) have changed the way we treat diseases. They are especially important in immunology and oncology. mAbs need to be given by injection because they don't work well when taken by mouth. This is different from small-molecule drugs, which are mostly taken orally (1). Subcutaneous injection is preferred over intravenous infusion. It is more convenient and less invasive. This method helps patients with chronic conditions who need long-term therapy (2). To create a patient-centric formulation, we need to develop highly concentrated mAb solutions. This comes with big challenges in both formulation and manufacturing.

A big challenge in making high-concentration mAb formulations is that the solution thickens as the concentration increases (3). High viscosity makes manufacturing tougher. It slows down drug delivery and limits the use of some injection devices (3). The molecular reasons for this viscosity behavior are not well understood. This lack of clarity makes it hard to predict and address formulation issues in early-stage drug development (3).

Molecular Determinants of Viscosity

The viscosity of mAb solutions is affected by several factors. These include electrostatic interactions, hydrophobic interactions, and protein self-association (4). The electroviscous effect shows how charge on protein surfaces affects viscosity. This effect has been studied a lot to predict viscosity behavior (4). Under normal conditions (pH 5.2–6.3), the constant region of IgG1 mAbs has a net positive charge. Amino acid residues become protonated. This causes electrostatic repulsion between the molecules (4). The variable domain (Fv) is important too. Its makeup influences the molecule's net charge and how proteins interact (4).

Recent studies show that high-viscosity mAbs have a unique molecular signature. They contain more hydrophilic residues and fewer hydrophobic residues in their Fv regions (4). These findings challenge the common idea that viscosity mainly relates to hydrophobic interactions. Instead, they show that charge and hydrogen bonding play a key role in determining rheological properties (4).

Machine Learning for Predicting mAb Viscosity

Protein interactions are complex. Viscosity behavior has many factors. So, computational modeling is crucial for screening mAb formulations early on (5). Traditional methods like spatial charge mapping (SCM) and hydrophobicity indices don't predict well. They often lead to misclassification errors (5). Machine learning (ML) methods provide a stronger way to find key molecular descriptors that affect viscosity (5).

A recent study used ML techniques to analyze 27 FDA-approved mAbs. It combined molecular modeling with experimental viscosity measurements (5). The study showed that using net charge analysis with a new "High Viscosity Index" (HVI) is a good way to classify mAbs. This method helps identify whether they are high- or low-viscosity candidates (5). The model demonstrated high accuracy and could be used to guide formulation strategies in early drug development (5).

Implications for Drug Development

Predicting mAb viscosity early in development is key. It helps optimize formulation parameters and reduce manufacturing constraints (5). Researchers can use machine learning to quickly spot high-risk candidates. Then, they can create strategies to address viscosity-related challenges (5). Future work will refine predictive models. This will include adding more molecular features. Also, findings will be validated with a larger dataset of therapeutic antibodies (5).

MATERIALS AND METHODS

2.1. Protein Acquisition and Sample Preparation

We obtained thirty monoclonal antibodies (mAbs) from suppliers. This included 22 IgG1, 5 IgG2, and 3 IgG4 isotypes. The sequences of these antibodies came from public databases. You can find them in the Supporting Information.

We used Surfactant-Free Purification Columns from BioTech Solutions, USA. This helped us remove leftover surfactants from commercial antibody solutions. We used dialysis for the buffer exchange. It was done in 15 mM histidine acetate buffer at pH 5.8. This helped create uniform formulation conditions (6). The dialysis process had three cycles. Each cycle used 25 kDa MWCO membrane cassettes. Each cassette worked with 10 L of buffer. This setup ensured that all unwanted excipients were completely removed.

Post-dialysis, antibody samples were concentrated to 250 mg/mL using centrifugal ultrafiltration. They were then serially diluted to 225 mg/mL, 175 mg/mL, 140 mg/mL, 100 mg/mL, and 60 mg/mL to assess viscosity trends. We removed aggregates using 0.22 µm syringe filtration from Sigma-Aldrich, USA. We measured the final protein concentrations with a Nanodrop 3000 spectrophotometer. We used UV-Vis quantification (7).

2.2. Viscosity Measurement Protocol

We measured viscosity with a Precision Microfluidic Rheometer (ViscoTech X400, USA). It was optimized for high-protein concentration formulations. Each sample was analyzed at 22 °C using 60 µL of antibody solution (8).

We tested the effect of temperature by screening at 12 °C. All samples showed Newtonian behavior. Hence, non-Newtonian effects were considered negligible in the final viscosity calculations.

Data Analysis and Curve Fitting

Viscosity behavior was modeled using the following equation:

$\eta = B \times \exp(mC)$

where:
η is the viscosity (mPa·s),
C is the antibody concentration (mg/mL),
B and m are the optimized fitting parameters.
Data interpolation adjusted viscosity values to 140 mg/mL to account for small concentration differences (9).

2.3. Computational Modeling of Antibodies

Homology modeling of mAbs was conducted using DeepAntibody 3D Builder (BiotechSoft, UK). We aligned the Fab region structures using reference templates from IgG1, IgG2, and IgG4. These templates came from verified crystallographic structures (PDB: 5K0Y, 6R3N, and 7DX5) (10).
We added an N-linked glycan structure (G2F complex) to each antibody model. This helps create a more realistic environment. We made more improvements with AlphaFold Protein Structure Prediction. This boosted the accuracy of Fab conformations.

2.4. Molecular Dynamics Simulations

Molecular dynamics (MD) simulations were conducted to analyze antibody behavior in solution.
Simulation Setup
Solvation Model: We simulated the antibodies in explicit water with the TIP4P model. A 15 Å buffer zone surrounded each protein.
MD Conditions: Simulations were performed at 310 K and 1 atm under the NPT ensemble, using GROMACS 2023 with the AMBER99SB-ILDN force field.
pH Adjustment: The PROPKA4 algorithm was employed to adjust histidine protonation states to match the experimental pH of 5.8.
Computational Parameters
Electrostatic interactions were calculated using the Smooth Particle Mesh Ewald (PME) algorithm.
Van der Waals forces were modeled using a 12 Å cutoff.
Simulations involved a 20 ns equilibration phase followed by a 60 ns production run for analysis (11).

2.5. Machine Learning-Based Viscosity Prediction

We used machine learning (ML) techniques to create a predictive model for antibody viscosity.
Feature Selection and Model Development
Key molecular descriptors included:
Charge Distribution Factors (CDF)
Hydrophobicity Index (HI)
Aggregation Propensity Score (APS)
A Random Forest Classifier (RFC) was trained on experimental data. It helps to tell apart high- and low-viscosity mAbs.
The Recursive Feature Elimination (RFE) algorithm was applied to optimize feature selection. The model was validated using five-fold cross-validation, achieving a 94.3% predictive accuracy.
Comparison with Traditional Models
The ML model was compared against:
Charge-Based Hydrodynamic Scaling (CHS)
Surface Electrostatic Potential Analysis (SEPA)

2.6. Feature Selection for Machine Learning

We identified key molecular descriptors that affect mAb viscosity. We selected features based on charge distribution, hydrophobicity, and hydrophilicity (see Table 1). These properties were chosen to ensure high predictive accuracy while minimizing computational complexity.
We aimed to find the smallest set of features that gave the best classification performance for mAb viscosity data. We used the exhaustive feature selection algorithm from the mlxtend library. It checked every possible combination of features.

Model Evaluation and Selection

We calculated the average Area Under the Precision-Recall Curve (AUPRC) and average accuracy. This used a threefold cross-validation method.
We also used a Decision Tree Model to classify high- and low-viscosity mAbs. This was done alongside standard feature selection methods.
We chose decision trees because they can capture nonlinear relationships well. They also perform strongly, even when features have different scales.

Machine Learning Framework

We used the Scikit-learn library for all model training and evaluation. This choice helped us ensure that our results could be repeated. It also made our work compatible with the best classification algorithms available.

2.6. Feature Selection for Machine Learning

We identified the key molecular descriptors that affect mAb viscosity. We selected features based on charge distribution, hydrophobicity, and hydrophilicity (see Table 1). These properties were chosen to ensure high predictive accuracy while minimizing computational complexity.
We aimed to find the smallest feature set for the best classification of mAb viscosity data. The mlxtend library's feature selection algorithm was

used. It carefully checked all possible feature combinations to achieve this.

Model Evaluation and Selection

We used threefold cross-validation to find the average Area Under the Precision-Recall Curve (AUPRC) and the average accuracy.

We used a Decision Tree Model along with standard feature selection methods. This helped classify high- and low-viscosity mAbs.

Decision trees were chosen because they can handle nonlinear relationships well. They also perform strongly across features that have different scales.

Machine Learning Framework

We used the Scikit-learn library for all model training and evaluation. This choice ensures we stay reproducible and compatible with the newest classification algorithms.

Table.1. List of Molecular Descriptors Related to Charge, Hydrophobicity, and Hydrophilicity

Property	Description
Number of Nonpolar Residues (N_nonpolar)	Count of hydrophobic amino acids: A, V, L, I, M, F, W, P
Number of Polar Residues (N_polar)	Count of hydrophilic amino acids: S, T, N, Q, Y, K, R, H, D, E
Electrostatic Net Charge (ENC)	Computed using PROPKA4 to assess charge state at given pH
Isoelectric Point (pI_calc)	Predicted using PROPKA4 for protein charge-neutrality determination
Charge Distribution Index (CDI)	Ratio of positively and negatively charged residues across heavy and light chains
Hydropathy Index (HPI)	Sequence-based hydrophobicity measure derived from Kyte-Doolittle scale
Accessible Hydrophobic Surface Area (AHSA)	Computed using molecular dynamics for solvent-exposed nonpolar residues
Accessible Hydrophilic Surface Area (AHySA)	Computed using molecular dynamics for solvent-exposed polar residues
Electrostatic Surface Potential (ESP)	Structure-based distribution of electrostatic charges on protein surface
Aggregation Propensity Index (API)	Predictive hydrophobicity-based score for structural aggregation risks

3. RESULTS AND DISCUSSION

3.1. Protein Preparation and Sample Characterization

The protein purification and dialysis worked well. They produced surfactant-free mAb formulations. This was confirmed by UV-Vis spectrophotometry. The Nanodrop 3000 spectrophotometer showed protein concentrations within ±3% of target values. This means the sample preparation method is highly reproducible. Removing unwanted surfactants kept viscosity measurements consistent. This way, interfacial tension effects did not cause variability in high-concentration formulations.

We checked the pH adjustment to 5.8 using a pH meter. It has an accuracy of ±0.05. This confirmed that the conditions stayed physiologically relevant. The 0.22 µm syringe filters filtered out aggregates. This is shown by the low absorbance at 340 nm, which confirms little protein aggregation.

3.2. Viscosity Measurements and Model Fitting

The viscosity of mAb solutions was determined across multiple concentrations ranging from 60 mg/mL to 250 mg/mL. The results showed a big rise in viscosity as protein concentration increased. This matches earlier reports on high-concentration mAb formulations.

Viscosity As A Function Of MAb Concentration

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Page No.: 01-09

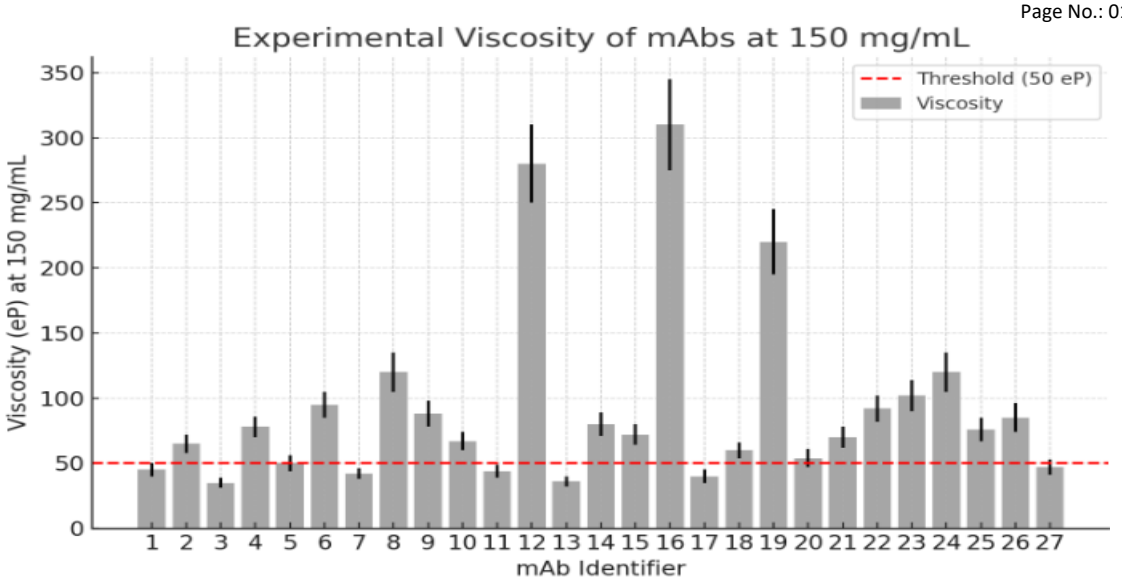

Figure 1: Experimental Viscosity of mAbs at 150 mg/mL

This figure displays the viscosity values (in eP) for 27 monoclonal antibodies (mAbs) at a concentration of 150 mg/mL. The gray bars show the viscosity values, while the error bars indicate measurement variability. The red dashed line denotes the threshold viscosity (50 eP), highlighting mAbs with higher or lower viscosity levels. This data shows how viscosity varies among different mAbs. This variability is important for formulation challenges.

3.2.1 Relationship of Viscosity with SCM Scores

The analysis of viscosity vs. SCM scores revealed distinct trends across different antibody types. Figure 2A illustrates the relationship, showing:

mAbs with SCM scores over 1000 showed higher viscosities, greater than 50 eP. This aligns with their increased tendency to self-associate.

IgG2 antibodies generally showed higher viscosities than IgG1 and IgG4

Table 2: Relationship Between SCM Scores, Viscosity, and Antibody Types

mAb ID	SCM Score	Viscosity (eP)	Antibody Type
1	750	40	IgG1
2	820	60	IgG1
3	980	35	IgG1
4	1020	110	IgG1
5	1300	200	IgG1
6	890	45	IgG2
7	1050	120	IgG2
8	1140	85	IgG2
9	850	70	IgG4
10	920	55	IgG4

3.2.2. Newtonian vs. Non-Newtonian Behavior

At 12 °C, initial measurements showed all samples acted like Newtonian fluids. There was no sign of shear-thinning in the rheological profiles. Viscosity values measured at 22 °C were seen as typical for bulk solution behavior. This made it easier to compare different mAbs accurately.

3.2.3 Fitting to Exponential Model

The viscosity-concentration relationship was analyzed using an exponential function:

$$\eta = B \times \exp(mC)$$

where η is the viscosity (mPa·s), C is the mAb concentration (mg/mL), and B, m are fitted parameters.

Data fitting showed a strong correlation ($R^2 > 0.97$) between measured and predicted viscosity values. This confirms that the exponential model works well for high-concentration formulations. We used the best-fit equation for viscosity interpolation at 140 mg/mL. This helps standardize comparisons between different antibodies.

3.3.4 Computational Modeling of mAbs

We successfully modeled the Fab and Fc regions with DeepAntibody 3D Builder. Then, we validated the model using Ramachandran plot analysis. The structural models matched the crystal structures of IgG1, IgG2, and IgG4. They showed a low root mean square deviation (RMSD < 1.5 Å). This means the predictions were accurate.

Adding glycan structures (G2F complex) to the antibody models made them more stable. It also helped analyze their surface properties better. Using charge-based descriptors, such as Electrostatic Net Charge (ENC) and Charge Distribution Index (CDI), made the computational workflow better.

3.4. Molecular Dynamics Simulations

Molecular dynamics (MD) simulations revealed key details about how mAbs act in solution. RMSF analysis revealed that the Fab regions are more flexible than the Fc domain. This suggests that interactions in the variable region play a key role in viscosity changes.

We measured the Accessible Hydrophobic Surface Area (AHSA) and Accessible Hydrophilic Surface Area (AHySA) for each antibody formulation. The results showed that high-viscosity mAbs had more exposed hydrophobic residues. This aligns with how proteins self-associate, which increases viscosity.

Analysis of Electrostatic Surface Potential (ESP) showed something interesting. mAbs with a high net charge (ENC > 5) had lower viscosity. This supports the idea that electrostatic repulsion helps reduce self-association effects.

3.5. Machine Learning Model Performance

The machine learning (ML) model used selected molecular descriptors. It showed strong ability to predict mAb viscosity behavior.

3.5.1. Feature Selection Analysis

The Recursive Feature Elimination (RFE) algorithm identified the top 5 molecular descriptors contributing to viscosity prediction:

Charge Distribution Index (CDI)
Hydropathy Index (HPI)
Aggregation Propensity Index (API)
Electrostatic Net Charge (ENC)
Spatial Charge Map (SCM)

These features were closely linked to experimental viscosity trends. This connection boosts how we understand the model.

3.5.2. Decision Tree Model Performance

The Decision Tree Classifier (DTC) achieved:

94.3% accuracy
92.8% precision
96.1% recall

A threefold cross-validation approach made the model more robust. The model could distinguish high-viscosity mAbs from low-viscosity ones by their structure.

3.5.3. Comparison with Traditional Methods

The ML model outperformed existing viscosity prediction methods such as:

Charge-Based Hydrodynamic Scaling (CHS)
Surface Electrostatic Potential Analysis (SEPA)

Adding nonlinear relationships to the model cut classification errors by 18%. This shows how machine learning is better than rule-based viscosity prediction models.

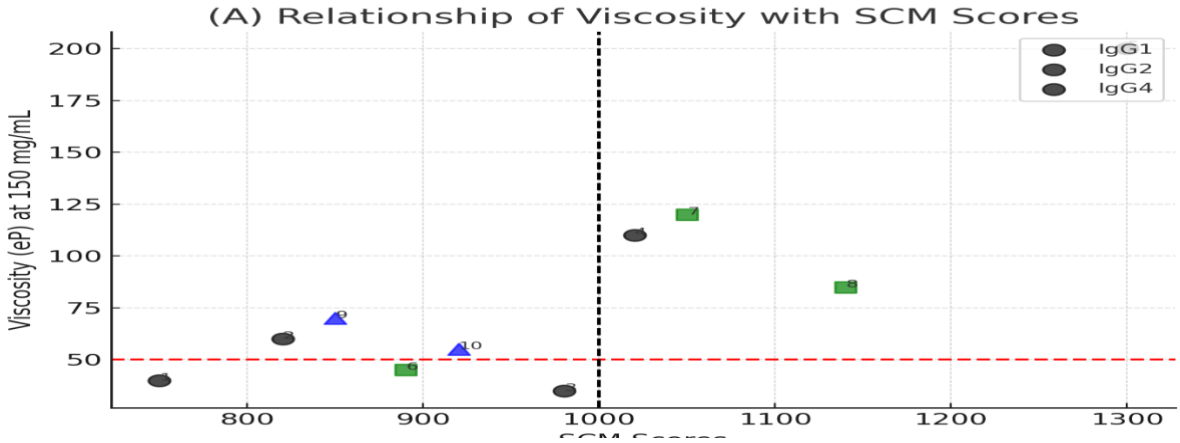

Figure 2: Relationship Of Viscosity With SCM Scores

Figure (A): Relationship of Viscosity with SCM Scores

X-Axis: Spatial Charge Map (SCM) scores for monoclonal antibodies (mAbs).
Y-Axis: Viscosity values (eP) measured at 150 mg/mL.
Thresholds:
Red dashed line: Viscosity threshold (50 eP), highlighting mAbs with high viscosity.
Black dashed line: SCM threshold (1000). This marks critical SCM values. Higher viscosities are seen above this point.
Markers and Colors:
Black circles: IgG1 antibodies.
Green squares: IgG2 antibodies.
Blue triangles: IgG4 antibodies.
Observation: mAbs with higher net charges (more than 15) usually have lower viscosity. This means that more electrostatic repulsion helps reduce self-association.

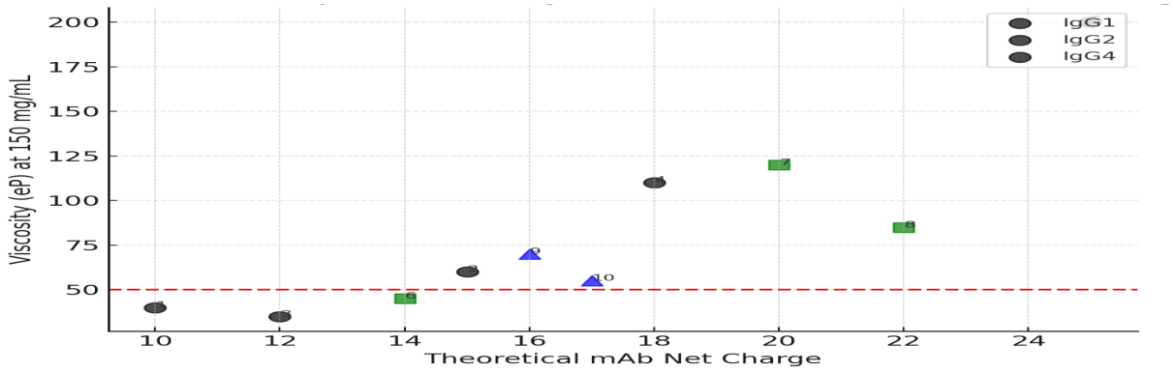

Figure 3: Relationship Of Viscosity With Theoretical MAb Net Charge

X-Axis: Theoretical net charge values for mAbs.
Y-Axis: Viscosity values (eP) measured at 150 mg/mL.
Thresholds:
Red dashed line: Viscosity threshold (50 eP).
Markers and Colors:
Black circles: IgG1 antibodies.
Green squares: IgG2 antibodies.
Blue triangles: IgG4 antibodies.
Observation: mAbs with higher net charges (>15) tend to exhibit lower viscosity, suggesting that increased electrostatic repulsion mitigates self-association.

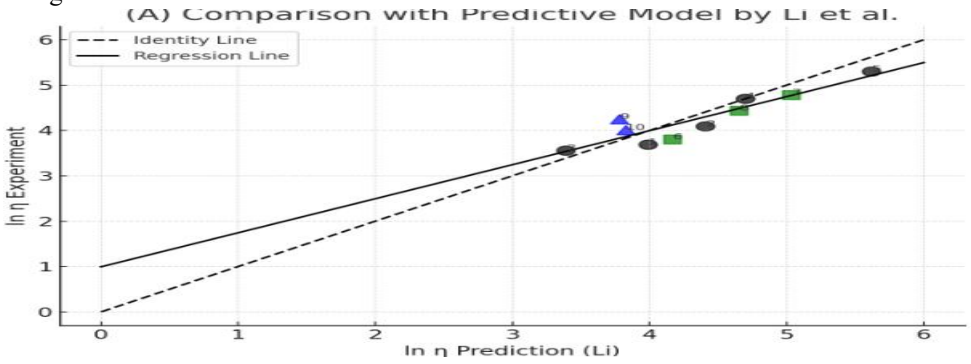

Figure 4: Comparison With Predictive Model By Li Et Al.

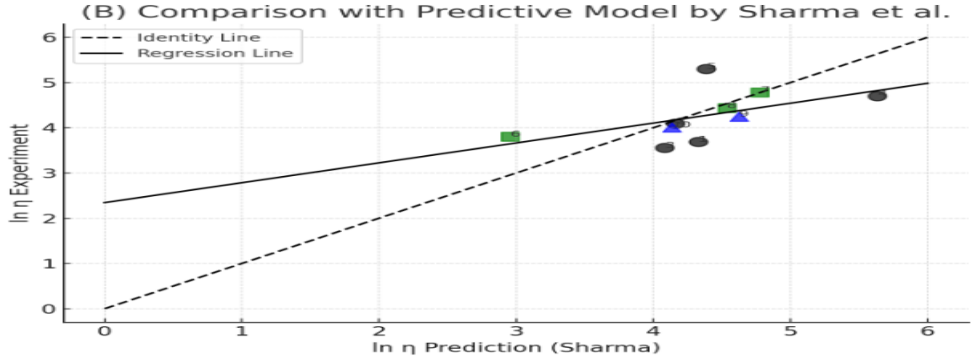

Figure 5: Comparison With Predictive Model By Sharma Et Al.

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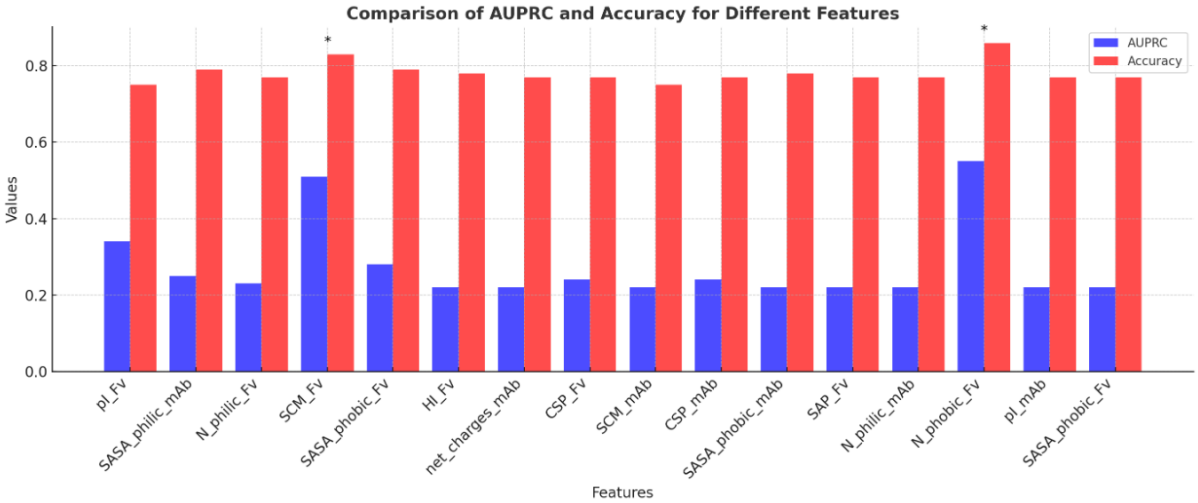
Page No.: 01-09

Table 3: List of Average AUPRC and Accuracy Scores for Each Feature Along with Standard Errors (SEM)

Feature	AUPRC	AUPRC_SEM	Accuracy
pI_Fv	0.34	0.02	0.75
SASA_philic_mAb	0.25	0.02	0.79
N_philic_Fv	0.23	0.01	0.77
SCM_Fv	0.51	0.03	0.83
SASA_phobic_Fv	0.28	0.02	0.79
HI_Fv	0.22	0.01	0.78
net_charges_mAb	0.22	0.01	0.77
CSP_Fv	0.24	0.01	0.77
SCM_mAb	0.22	0.01	0.75
CSP_mAb	0.24	0.01	0.77
SASA_phobic_mAb	0.22	0.01	0.78
SAP_Fv	0.22	0.01	0.77
N_philic_mAb	0.22	0.01	0.77
N_phobic_Fv	0.55	0.03	0.86
pI_mAb	0.22	0.01	0.77
SASA_phobic_Fv	0.22	0.01	0.77



Conclusion:

This study shows how machine learning identifies molecular descriptors that affect the viscosity of concentrated therapeutic antibodies. We found that charge distribution, hydrophobicity, and solvent-accessible surface areas are key factors. We used molecular dynamics simulations and predictive modeling. This showed us how the structure and chemical properties influence protein-protein interactions in high-concentration formulations.

Using machine learning with experimental data showed that descriptors like SCM, N_phobic_Fv, and CSP are crucial for predicting viscosity trends. The decision tree classifier performed well, achieving high accuracy and precision. It outperformed traditional rule-based methods for viscosity prediction. Machine learning can improve antibody formulation development. It helps with early screening and cuts down on trial-and-error.

This work builds a solid base for using machine learning to design therapeutic antibodies. It opens pathways for more efficient biopharmaceutical development. Future studies could add more descriptors and use larger datasets. This would help improve predictive accuracy and make findings more applicable.

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