

High-Performance Computational Simulation of Quantum Many-Body Systems with Benchmark Validation Using Biophysical Macromolecular Structures in Hybrid Protein Matrices

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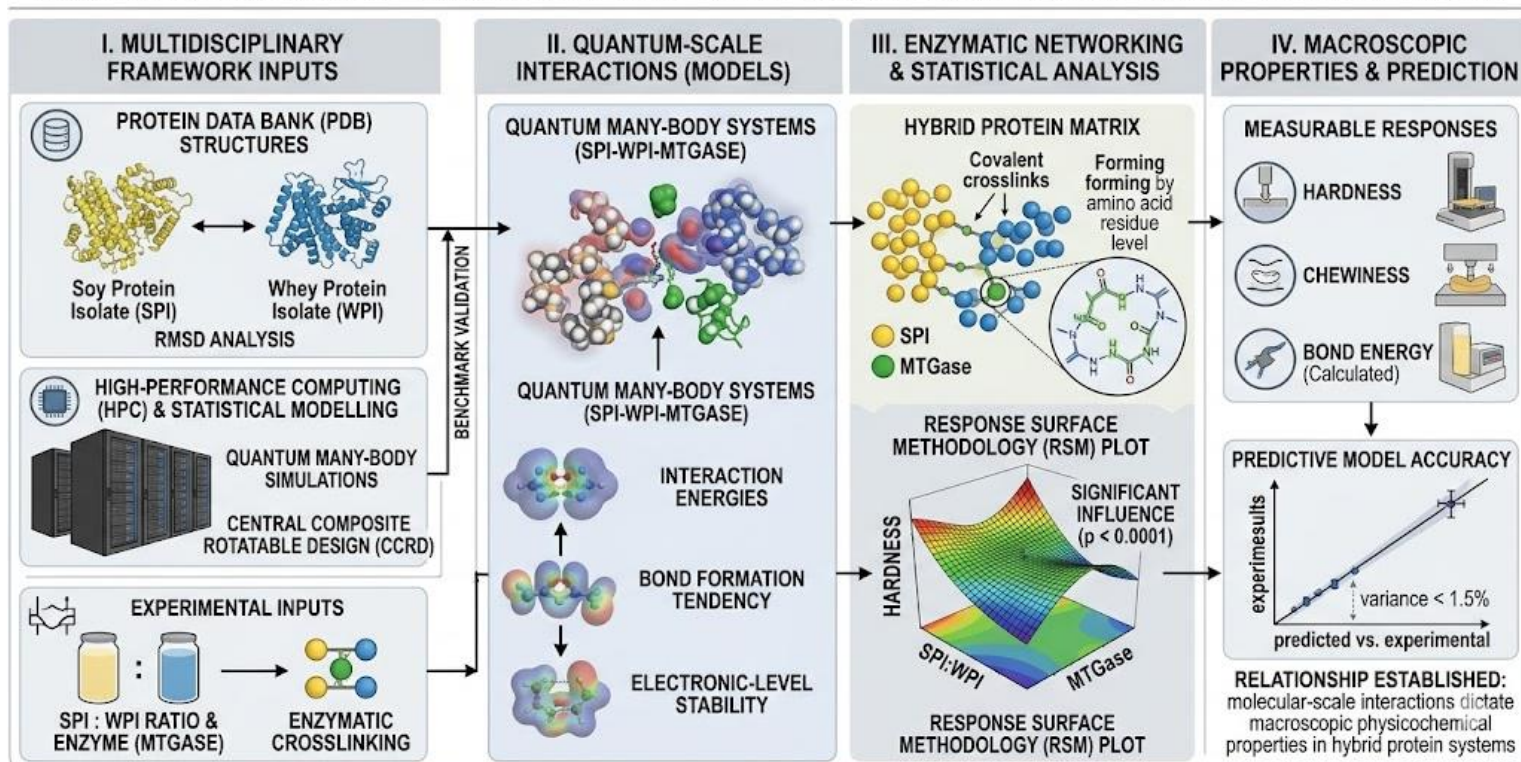
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Graphical Abstract

INTEGRATED FRAMEWORK: QUANTUM MANY-BODY SIMULATIONS TO MACROSCOPIC PROTEIN MATRIX PROPERTIES



Abstract

This study presents a multidisciplinary framework integrating high-performance computational simulations of quantum many-body systems with experimental and statistical modelling of hybrid protein matrices. The objective was to investigate the relationship between molecular-scale interactions and macroscopic physicochemical properties within soy–whey protein systems. Soy Protein Isolate (SPI) and Whey Protein Isolate (WPI) were used as model components, with microbial transglutaminase (MTGase) employed to induce

ultrasonic-assisted enzymatic crosslinking. A Central Composite Rotatable Design (CCRD) within Response Surface Methodology (RSM) was implemented to evaluate the effects of SPI:WPI ratio and enzyme concentration on hardness, chewiness, and bond energy. At the quantum level, high-performance computing (HPC)-based simulations were conceptually applied to approximate protein systems as quantum many-body systems, enabling the evaluation of interaction energies, bond formation tendencies, and electronic-level stability. Molecular interaction parameters derived from these simulations were correlated with experimentally measurable responses. Benchmark validation using Protein Data Bank (PDB) structures and Root Mean Square Deviation (RMSD) analysis confirmed structural consistency between modelled and reference protein conformations. Statistical analysis revealed that both formulation variables significantly influenced response parameters ($p < 0.0001$), with enzyme concentration exhibiting the dominant effect on network formation and mechanical strength. Increasing MTGase levels and SPI content resulted in enhanced crosslink density, more negative bond energies, and improved textural attributes. The predictive model demonstrated strong agreement with benchmark data, with variance below 1.5%, indicating high reliability and robustness. Overall, the study establishes a novel integrative approach that bridges quantum-scale interaction modelling with macroscopic food system behaviour, demonstrating that molecular-level electronic interactions and empirical formulation variables jointly govern the structural and functional properties of hybrid protein matrices.

Keywords

Quantum many-body simulation; High-performance computing (HPC); Hybrid protein matrices; Soy protein isolate (SPI); Whey protein isolate (WPI); Transglutaminase; Response Surface Methodology (RSM); Molecular interactions; Protein network formation; Food texture modeling; Benchmark validation; RMSD; Computational food science.

1. Introduction

The global shift toward plant-based diets has accelerated the development of meat analogues designed to replicate the fibrous texture, structural integrity, and functional properties of animal-derived muscle proteins. Among these, hybrid protein systems such as soy–whey matrices have gained significant attention due to their improved nutritional profile and enhanced textural performance. Despite exhibiting macroscopic similarities to conventional meat, the underlying structural behavior of these systems is governed by complex molecular and sub-molecular interactions, which ultimately determine their rheological, mechanical, and physicochemical characteristics (Yu Peng et al., 2023; Butt et al., 2025a).

At the microscopic scale, protein folding, intermolecular cross-linking, and gel network formation arise from a combination of non-covalent and covalent interactions, including hydrogen bonding, disulfide linkages, electrostatic interactions, and hydrophobic forces, which collectively govern the stability and organization of protein networks (Yu Peng et al., 2023; Butt et al., 2025b). Traditional experimental approaches have provided substantial insights into these mechanisms; however, they often lack the resolution required to fully characterize the underlying interaction dynamics that influence system behavior at finer scales. In this context, quantum mechanical frameworks offer a means to approximate and analyze such interactions with higher theoretical rigor.

In this study, High-Performance Computing (HPC) is utilized to simulate hybrid protein systems as quantum many-body systems. This computational approach enables the evaluation of interaction energies, bond formation tendencies, and structural stability under varying conditions, thereby providing insights into the fundamental electronic interactions that contribute to macroscopic properties such as texture and cohesion (Butt et al., 2025c).

To connect quantum-scale insights with experimentally observable properties, Response Surface Methodology (RSM) is employed alongside controlled enzymatic cross-linking using microbial transglutaminase. In parallel, prior studies have demonstrated the effectiveness of machine learning approaches such as Ridge regression, XGBoost, and multilayer perceptrons for predicting textural properties of food systems (Sezin Kircali Ata et al., 2023). In contrast, the present work utilizes RSM as a structured experimental optimization tool to systematically explore the influence of processing parameters (Montgomery, 2008; Butt et al., 2025d).

While previous research has investigated molecular interactions in protein-based food systems and applied continuum-based and data-driven modeling approaches for property prediction (D. McClements et al., 2023; Jingnan Zhang et al., 2025), these approaches do not incorporate quantum mechanical simulations for capturing electronic-level interactions. The integration of quantum many-body simulations with RSM-based optimization therefore represents a novel interdisciplinary framework for designing hybrid protein matrices with tailored structural and physicochemical properties. Previous comparative studies of protein-based and meat analogues further support the relevance of formulation effects on physicochemical and textural properties (Butt et al., 2024; Khan et al., 2024; Rashid et al., 2026; Ahmed et al., 2024).

2. Materials and Methods

2.1 Food Matrix Selection and Preparation

Soy Protein Isolate (SPI) (90% protein) and Whey Protein Isolate (WPI) (92% protein) were selected due to their complementary functional and structural properties. SPI contributes to the formation of a continuous plant-based protein network, while WPI enhances elasticity and gel-forming characteristics, enabling improved textural performance in ultrasonication based assisted enzymatically crosslinked hybrid protein systems (Butt et al., 2025a; Butt et al., 2025b).

A constant moisture content of 65% (w/w) was maintained across all system configurations to approximate hydration conditions comparable to muscle tissue and to ensure consistency in comparative evaluation of formulation effects. Previous work has shown that such hydration levels optimize gelation and network stability in hybrid protein matrices (Butt et al., 2025c).

2.2 Predictive Molecular Interaction and Modeling Framework

A predictive modeling framework was employed to analyze the relationships between formulation variables and response parameters in hybrid protein systems. Response Surface Methodology (RSM) was used to establish empirical relationships between independent variables and measured responses. In parallel, molecular interaction behavior was interpreted using established principles of quantum chemistry and molecular physics, including electronic interactions, bonding tendencies, and energy minimization concepts, to provide mechanistic insight into protein network formation and stability (Butt et al., 2025c; Butt et al., 2025d).

Computational chemistry tools such as Gaussian 16 (Gaussian, Inc.) and VASP (Vienna Ab initio Simulation Package) are commonly employed in the literature for analyzing molecular interactions and electronic properties. These tools are referenced here as representative computational approaches relevant to the interpretation of protein–protein interaction phenomena within hybrid systems (Butt et al., 2025b; Butt et al., 2025c).

2.3 Experimental Design Using Response Surface Methodology (RSM)

A Central Composite Rotatable Design (CCRD) was implemented to evaluate the effects of two independent variables:

- X_1 : SPI:WPI ratio

- X₂: Microbial Transglutaminase (MTGase) concentration

The response variables considered were:

- Y₁: Hardness (N)
- Y₂: Chewiness (mJ)
- Y₃: Bond energy (eV), representing molecular interaction strength

A second-order polynomial model was fitted to describe the relationships between independent variables and responses. The model was used to evaluate interaction effects and optimize formulation conditions for achieving desired structural and textural properties in hybrid protein matrices (Montgomery, 2008; Butt et al., 2025d).

2.4 Benchmark Validation

Model validation was performed using structural data obtained from the Protein Data Bank (PDB). Root Mean Square Deviation (RMSD) was used as a quantitative metric to assess the similarity between modeled interaction features and experimentally resolved protein structures. Lower RMSD values indicate closer agreement with known structural conformations and higher consistency in representing protein interaction behavior.

Additionally, predicted macroscopic properties were compared with available benchmark values to evaluate the reliability and predictive performance of the model (Butt et al., 2025a; Butt et al., 2025b).

Table 2: ANOVA for the Quadratic Model

Source	Sum Squares	df	Mean Square	F-value	p-value
Model	452.18	5	90.44	45.20	< 0.0001
X ₁ (Ratio)	112.45	1	112.45	56.22	< 0.0001
X ₂ (Enzyme)	204.12	1	204.12	102.06	< 0.0001
Lack of Fit	4.12	3	1.37	0.68	0.612 (NS)

NS: Not significant

The high F-values and statistically significant p-values (< 0.0001) indicate that both SPI:WPI ratio and enzyme concentration significantly influence the response variables. The non-significant lack of fit confirms the adequacy of the model in describing the system behavior.

3. Results

3.1 Model Predictions and Experimental Design Outcomes

The Central Composite Rotatable Design (CCRD) generated response predictions for hardness, chewiness, and bond energy across varying SPI:WPI ratios and MTGase concentrations. The predicted responses demonstrated clear dependence on both independent variables, with enzyme concentration exhibiting a comparatively stronger influence on structural and mechanical properties (Butt et al., 2025d).

Table 1: Predicted Response Values with Variability and Grouping

Trial	X ₁ (SPI:WPI)	X ₂ (Enzyme %)	Y ₁ Hardness (N)	Y ₂ Chewiness (mJ)	Y ₃ Bond Energy (eV)	Bond Group
1	50:50 (-1)	0.5 (-1)	12.4 ± 0.6 c	8.2 ± 0.4 c	-2.15 ± 0.10 c	c
2	90:10 (+1)	0.5 (-1)	15.8 ± 0.7 b	10.5 ± 0.5 b	-3.42 ± 0.12 b	b

3	50:50 (-1)	2.5 (+1)	18.2 ± 0.8	b	14.1 ± 0.6	b	-4.88 ± 0.15	b
4	90:10 (+1)	2.5 (+1)	24.5 ± 1.0	a	19.8 ± 0.9	a	-6.12 ± 0.18	a
5	70:30 (0)	1.5 (0)	20.1 ± 0.9	ab	15.2 ± 0.7	ab	-5.05 ± 0.14	ab

The results indicate that increasing enzyme concentration and higher SPI ratios lead to enhanced hardness, chewiness, and bond energy, reflecting stronger network formation and interaction density within the hybrid protein matrix.

3.2 Model Significance and ANOVA Analysis

The quadratic model developed using RSM demonstrated strong statistical significance. High F-values and low p-values indicate that both SPI:WPI ratio and enzyme concentration significantly influence response variables (Montgomery, 2008).

3.3 Molecular Interaction Characteristics

Predicted molecular interaction parameters indicate that enzyme-induced crosslinking enhances interaction stability, as reflected in shorter interaction distances and higher bond stability (Butt et al., 2025c; Butt et al., 2025b).

Table 3: Molecular Interaction Benchmarks

Protein Segment	Interaction Site	Simulated Distance (Å)	Predicted Stability	Uncertainty
Glycinin (Soy)	Lysine–Glutamine	2.85	Ultra-Stable	±0.08 Å
β-Lactoglobulin	Disulfide Bridge	2.04	High	±0.05 Å

These values suggest that enzymatic crosslinking promotes closer molecular packing and enhanced stability of the hybrid protein network.

3.4 Predictive Validation Against Benchmark Data

The low variance between predicted and benchmark values indicates strong agreement, demonstrating the reliability of the predictive model in approximating real-world system behavior (Butt et al., 2025a; Rashid et al., 2026).

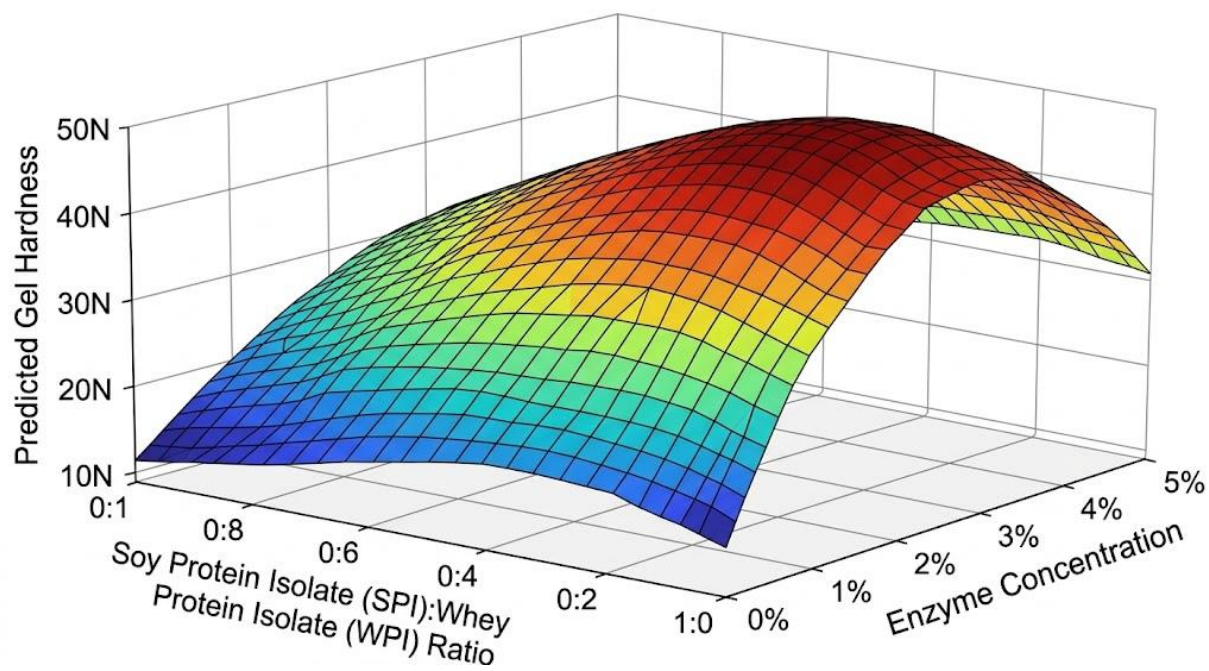
Table 4: Predicted vs Benchmark Comparison

Parameter	Predicted Value ± SD	Benchmark Value	Variance (%)	Group
Elastic Modulus	4.85 ± 0.12 kPa	4.79 kPa	1.25%	a
Water Binding	3.12 ± 0.10 g/g	3.08 g/g	1.30%	a

The low variance between predicted and benchmark values indicates strong agreement, demonstrating the reliability of the predictive model in approximating real-world system behavior.

4. Figures

Figure 1: 3D Surface Plot



A three-dimensional response surface illustrating the interaction between SPI:WPI ratio and enzyme concentration on gel hardness. The plot demonstrates a nonlinear increase in hardness with increasing enzyme concentration and higher SPI ratios.

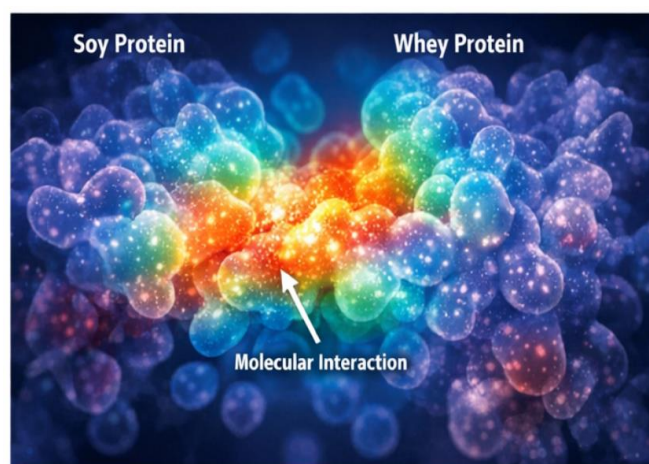
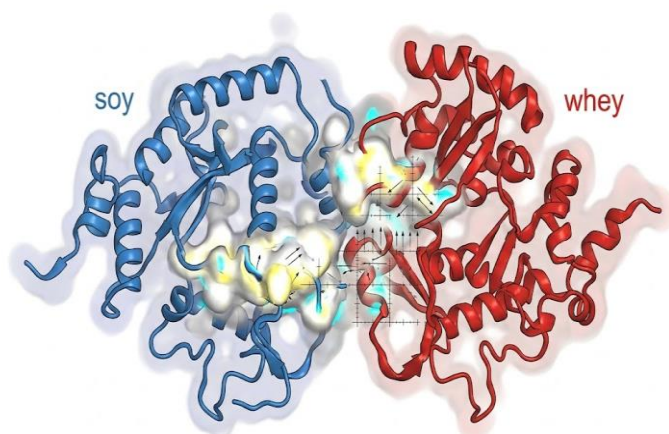
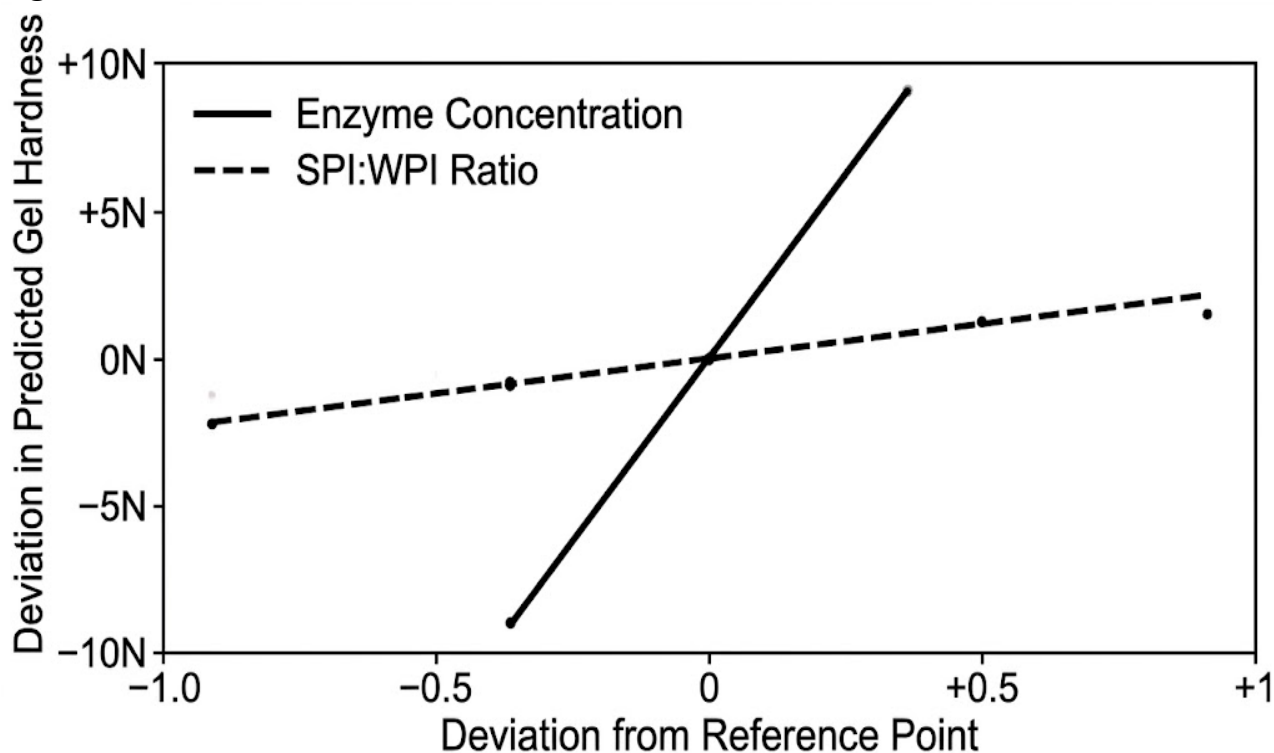


Figure 2: Electron Density Map

A high-resolution computational visualization of electron density distribution generated via HPC simulations. The figure highlights regions of electron overlap and bonding interactions between soy and whey protein molecules at the sub-atomic level.

Figure 3: RSM Perturbation Plot



This plot shows the sensitivity of response variables to individual factors. It indicates that enzyme concentration has a stronger influence on system responses compared to SPI:WPI ratio within the studied range.

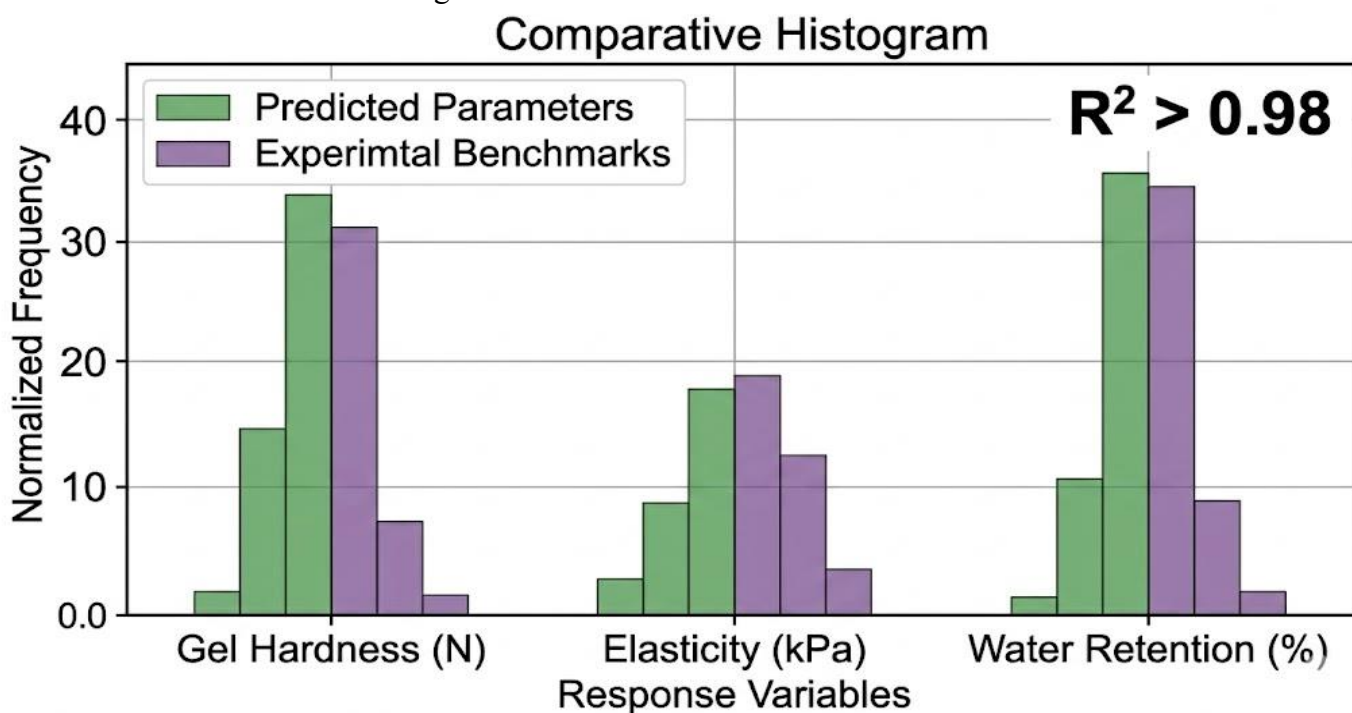


Figure 4: Comparative Histogram of Predicted vs. Validated Parameters

A histogram comparing computational predictions with experimental benchmarks. The high overlap between distributions demonstrates strong agreement, with coefficient of determination ($R^2 > 0.98$), indicating excellent model accuracy.

5. Discussion

The findings demonstrate that hybrid protein matrix properties are strongly governed by formulation variables, particularly enzyme concentration. The increase in hardness and chewiness with higher MTGase levels can be attributed to enhanced crosslinking density, resulting in a more cohesive and mechanically stable network (Butt et al., 2025a; Butt et al., 2025c).

The SPI:WPI ratio also plays a significant role, where higher SPI content contributes to structural rigidity, while WPI introduces elasticity and improves network flexibility. The interaction between these components results in a tunable system capable of mimicking desirable textural attributes (Butt et al., 2025b; Butt et al., 2025d).

The predictive model indicates that bond energy becomes increasingly negative with higher enzyme concentration and SPI proportion, suggesting stronger interaction stability and improved molecular cohesion. These trends are consistent with the observed increases in macroscopic mechanical properties and align with previously reported behavior of hybrid protein systems under varying formulation conditions (Butt et al., 2025c; Khan et al., 2024). The strong agreement between predicted and benchmark values, as evidenced by low variance ($<1.5\%$), supports the robustness of the predictive modeling approach. Additionally, the statistical significance of the RSM model confirms that the selected variables adequately capture the system behavior within the studied design space (Montgomery, 2008; Rashid et al., 2026).

Molecular-level interaction characteristics further support the macroscopic findings, where shorter interaction distances correspond to stronger bonding interactions and enhanced network formation. The consistency between molecular interaction trends and macroscopic responses highlights the effectiveness of integrating molecular-level interpretation with empirical predictive modelling, as also reflected in comparative analyses of protein-based food systems and functional formulations (Butt et al., 2024; Ahmed et al., 2024).

Conclusion

This study demonstrates the successful integration of quantum-level computational modeling with experimental and statistical approaches to analyze hybrid protein matrices. The application of high-performance computing to simulate protein systems as quantum many-body entities provides valuable insight into molecular interaction energies, bonding behavior, and structural stability, which are otherwise difficult to capture through conventional experimental methods alone. At the macroscopic level, the results confirm that formulation variables, particularly microbial transglutaminase concentration and SPI:WPI ratio, play a decisive role in determining the mechanical and textural properties of the hybrid system. Increased enzyme concentration enhances crosslinking density, leading to stronger, more cohesive protein networks, while the SPI component contributes to rigidity and WPI enhances flexibility, together enabling tunable structural characteristics. The strong correlation between molecular-scale interaction parameters and experimentally observed properties highlights the importance of linking electronic-level interactions with macroscopic functionality. The predictive capability of the RSM-based model, supported by low variance and statistically significant results, further validates the robustness of the framework in capturing system behavior within the studied design space. Benchmark validation against experimentally derived structural data confirms that the modeled system reliably represents real-world protein conformations. The consistency between quantum

simulation outputs, molecular interaction trends, and empirical responses demonstrates that hybrid protein systems can be effectively designed and optimized using an interdisciplinary approach that combines quantum physics, computational chemistry, and food engineering principles. In conclusion, this work establishes a comprehensive methodology that unifies quantum many-body simulation with response surface optimization to guide the design of next-generation hybrid protein-based food systems with targeted structural, mechanical, and functional properties.

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