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COMPUTATIONAL INVESTIGATION OF ENZYME–SUBSTRATE INTERACTIONS USING STRUCTURAL BIOINFORMATICS AND MOLECULAR DYNAMICS SIMULATIONS

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Abstract

Background: *Enzyme–substrate interactions are central to metabolic regulation, biological catalysis, and therapeutic discovery. Structural bioinformatics, molecular docking, and molecular dynamics (MD) simulations provide complementary means of investigating substrate recognition, interaction patterns, and conformational stability.*

Aim: *To characterize binding patterns, key interacting residues, and structural stability in three enzyme–substrate systems using a comparative computational workflow.*

Methods: *Three enzyme–substrate systems were selected from public structural databases. After molecular preparation, docking and contact analysis were performed, followed by 100-nanosecond MD simulations of selected complexes. Protein backbone root-mean-square deviation (RMSD), residue root-mean-square fluctuation (RMSF), radius of gyration (Rg), hydrogen bonds, and estimated binding free energies were evaluated.*

Results: *Predicted docking scores ranged from −6.8 to −9.4 kcal/mol, with the top-ranked system showing approximately 5–8 hydrogen bonds in the initial interaction analysis. Simulations suggested relatively stable conformational regimes after about 20–35 ns. Average backbone RMSD was 1.5–2.8 Å, interacting-residue RMSF was commonly 0.8–2.0 Å, and Rg changed by approximately 1–3% relative to the equilibrated baseline. Estimated binding free energies ranged from −25 to −42 kcal/mol. Hydrogen bonding, hydrophobic contacts, and electrostatic interactions contributed to modeled complex persistence.*

Conclusion: *The combined approach offers a useful structural framework for comparing enzyme–substrate recognition and complex stability. Docking and end-state energy estimates are predictive rather than experimental measures of affinity, and the biological relevance of the modeled complexes requires experimental validation.*

1. INTRODUCTION AND REVIEW OF LITERATURE

1.1 Background of the Study

Enzymes accelerate biochemical reactions while discriminating among chemically similar molecules. Their specificity depends on active-site geometry, molecular recognition, solvation, and the arrangement of catalytic groups. Substrate association is therefore more complex than the formation of a favorable static contact pattern: the enzyme must often position the substrate in an environment compatible with the subsequent chemical step. The magnitude of enzyme-catalyzed rate enhancement and the contribution of electrostatic preorganization underscore this distinction (Wolfenden & Snider, 2001; Warshel et al., 2006).

Atomic structures deposited in the Protein Data Bank and modern protein-structure prediction methods have greatly expanded the structural information available for computational studies (Berman et al., 2000; Jumper et al., 2021). However, a structure is a snapshot of a dynamic molecular ensemble. Computational methods are thus valuable when used together: docking proposes plausible binding orientations, whereas MD explores their behavior over time.

The first structural challenge is to distinguish a substrate-binding pose that merely fits within a pocket from a binding arrangement capable of supporting biological recognition. A predicted favorable docking score can arise from extensive contact area, yet catalytically useful association also depends on orientation, protonation and the spatial alignment of chemically reactive groups. These distinctions motivate the combination of docking, interaction analysis and molecular dynamics used in the present work.

Examining three systems within a common computational framework allows broad descriptors to be compared while preserving the distinction between chemical recognition and catalytic function. In particular, the investigation considers docking energetics, the relative persistence of contact types, overall protein displacement, local residue mobility and compactness as different views of one structural process.

1.2 Molecular Basis of Enzyme–Substrate Recognition

Enzyme recognition may involve hydrogen bonds, hydrophobic packing, ionic interactions, and changes in the conformation of both binding partners. Koshland (1958) proposed induced fit, while later energy-landscape models emphasized conformational ensembles and pre-existing binding-competent states (Ma et al., 1999). Hammes et al. (2009) explained that induced fit and conformational selection may coexist, with their contributions determined by kinetic pathways rather than by one static structure.

Experimental work has linked enzyme motions to catalysis and revealed transient conformations not always captured in conventional structures (Eisenmesser et al., 2005; Henzler-Wildman et al., 2007; Fraser et al., 2009). These findings support an interpretation of substrate binding that incorporates both residue-level contacts and conformational flexibility. Importantly, a persistent bound pose is not, by itself, evidence of catalytic turnover.

Hydrogen bonds contribute orientation-sensitive interactions, whereas hydrophobic packing can stabilize the substrate in a complementary binding cavity. Electrostatic attraction or repulsion may further influence recognition and transition-state organization. Each interaction type depends on the local environment; a hydrogen bond exposed to water, for example, has a different energetic context from one buried in an active site.

Dynamic recognition is especially relevant where binding involves loops, lids or flexible side chains. A modest global RMSD may coexist with active-site rearrangement, and a locally mobile residue may remain functional if its motion supports substrate positioning. Consequently, both whole-protein and interface-focused measurements are required to interpret a bound complex.

1.3 Computational Methods for Interaction Analysis

Molecular docking searches for geometrically and energetically plausible substrate poses within an enzyme binding site. Programs such as AutoDock and AutoDock Vina provide efficient screening and structural hypotheses, while newer implementations have improved

sampling and scoring options (Morris et al., 2009; Trott & Olson, 2010; Eberhardt et al., 2021). Preparation quality, protonation states, cofactors, and receptor flexibility materially affect results. Docking scores should therefore be treated as approximate ranking functions, not direct measurements of binding affinity (Warren et al., 2006; Ferreira et al., 2015).

MD applies a molecular-mechanics model to investigate the evolution of protein–substrate systems in a simulated environment. Established theoretical and practical developments have enabled studies of protein conformational change and molecular recognition (Karplus & McCammon, 2002; Dror et al., 2012). Simulation analysis commonly uses RMSD for structural drift, RMSF for residue flexibility, Rg for compactness, and contact persistence to assess the behavior of a proposed complex. Agreement among these measures provides stronger evidence of structural persistence than any single metric.

The main advantage of an integrated computational approach is that the output of one method can be assessed using a different physical descriptor. Docking provides candidate geometries; contact analysis identifies plausible molecular determinants; MD probes whether a proposed complex remains structurally coherent; and end-state energetic calculations estimate the favorability of modeled association. No single stage independently establishes enzyme specificity or catalytic competence.

1.4 Review of Literature

1.4.1 Structural recognition and molecular flexibility

Research on functional enzyme dynamics demonstrates that proteins can visit alternative conformations relevant to recognition and catalysis (Eisenmesser et al., 2005; Henzler-Wildman et al., 2007). Fraser et al. (2009) further showed the importance of otherwise hidden structural states. Taken together, these studies indicate that analysis of enzyme–substrate complexes should extend beyond a single crystallographic or docked pose to include conformational rearrangements and the persistence of catalytically relevant contacts.

1.4.2 Docking and structure-guided modeling

Comparative testing has shown substantial variability among docking algorithms and scoring functions (Warren et al., 2006). Methodological reports on AutoDock4, Vina, and Vina 1.2.0 document improvements in search and pose generation but do not eliminate uncertainty arising from solvation and protein motion (Morris et al., 2009; Trott & Olson, 2010; Eberhardt et al., 2021). Consequently, docking is most informative when it is followed by interaction profiling and dynamic evaluation rather than interpreted as a definitive affinity assay.

1.4.3 Dynamics and molecular simulation

Long-timescale simulations have revealed protein motions that are difficult to infer from static models (Shaw et al., 2010), while subsequent reviews describe MD as a molecular-level complement to experiments (Dror et al., 2012; Hollingsworth & Dror, 2018). Software advances, including AMBER, GROMACS, and OpenMM, have made such investigations more accessible (Case et al., 2005; Hess et al., 2008; Abraham et al., 2015; Eastman et al., 2017). Nevertheless, predicted behavior depends on force fields, water representation, electrostatics, and sampling choices (Jorgensen et al., 1983; Darden et al., 1993; Huang et al., 2017).

1.4.4 Binding free-energy estimation

End-state approaches combining molecular mechanics with continuum-solvent models offer an economical means of comparing modeled binding energetics (Kollman et al., 2000). MMPBSA.py facilitated practical trajectory-based calculations (Miller et al., 2012), and Genheden and Ryde (2015) detailed the strengths and weaknesses of MM/PBSA and MM/GBSA. Binding free-energy prediction remains sensitive to sampling, solvation, conformational entropy, and method selection; calculated values should therefore not be equated with experimentally determined affinities (Mobley & Gilson, 2017).

1.5 Research Problem and Gap

Although docking, MD, and free-energy analysis are widely used, interpreting them in isolation can produce misleading conclusions. A low docking score may be associated with an

unstable pose, while low RMSD does not establish biochemical catalysis. A concise, comparable workflow is needed to evaluate the same enzyme–substrate systems through binding geometry, residue contacts, conformational stability, and approximate energetics, while acknowledging uncertainty in each method (Warren et al., 2006; Genheden & Ryde, 2015). A further reporting challenge arises when comparisons use summary statistics without presenting underlying trajectory-level distributions. Grouped ranges can describe the magnitude of observed behavior but cannot identify which complex produced each endpoint, quantify convergence or support formal significance testing. The present manuscript therefore focuses its numerical interpretation on the study-level values actually recorded in the supplied research material.

1.6 Aim and Specific Objectives

The aim of this study is to characterize and compare substrate recognition and the simulated structural stability of three enzyme–substrate complexes using structural bioinformatics, docking, and 100-ns MD simulations. The specific objectives are to:

1. Prepare and assess the structural models of three enzyme–substrate systems.
2. Identify plausible substrate-binding poses and important active-site interactions.
3. Compare RMSD, RMSF, Rg, and hydrogen-bond persistence across MD trajectories.
4. Interpret estimated binding free energies alongside structural descriptors and methodological limitations.

1.7 Significance of the Study

By combining complementary computational descriptors, the study offers a structured basis for identifying residues and interaction networks that merit further investigation. The results can help prioritize hypotheses for mutagenesis, enzyme engineering, mechanistic experiments, and structure-guided screening. Such applications depend on considering the chemistry of each enzyme–substrate pair and confirming key predictions experimentally.

The resulting synthesis is most useful as a basis for generating experimentally testable hypotheses. For example, residues involved in persistent polar contacts can be prioritized for site-directed mutagenesis, whereas flexible pocket segments can be considered in conformational sampling and engineered specificity studies. The broader significance lies in combining physically distinct measurements rather than reducing recognition to one score.

1.8 Scope and Limitations

The investigation is restricted to three modeled enzyme–substrate systems and selected 100-ns simulation trajectories. The descriptors characterize behavior under the chosen structural preparation, force field, solvent model, and simulation conditions; they cannot establish complete conformational convergence or reaction kinetics. Docking scores and MM/PBSA- or MM/GBSA-type estimates are method-dependent predictions, and their numerical values should not be compared as if derived from the same thermodynamic definition. Experimental binding and catalytic assays remain necessary to assess biological function.

2.MATERIALS AND METHODS

2.1 Research design and comparative framework

We organized the study as a comparative structural-bioinformatics investigation of three enzyme–substrate systems. The workflow combined structure retrieval and inspection, substrate preparation, molecular docking, interaction profiling, molecular dynamics (MD), trajectory descriptors and approximate binding-energy estimation. Comparisons were intended to use consistent analytical definitions across the selected complexes so that binding geometry could be considered alongside subsequent modeled structural behavior.

The analytical units were three protein–substrate complexes drawn from public structural resources. Protein Data Bank (PDB) entries supplied the structural basis, while suitable chemical databases provided corresponding substrate structures. Individual protein names, ligand identifiers and accession codes were not specified in the study summary; consequently, sequence-specific or residue-number-specific assignments are not reported.

2.2 Protein and substrate structural preparation

Protein coordinate files were inspected for missing atoms, incomplete residues, alternate atom conformations and biologically relevant components such as cofactors and metal ions. Structural preparation included removal of unnecessary components where appropriate, addition of hydrogen atoms and assignment of protonation states consistent with the intended simulation environment. Substrate geometry was examined for chemical connectivity, stereochemistry, formal charge and functional groups before any required optimization.

These preparation decisions are consequential because changes in protonation or retained cofactors may affect the directionality and energetic contribution of active-site interactions. The comparison was therefore framed around chemically plausible substrate placement rather than geometric fit alone.

2.3 Molecular docking protocol

AutoDock Vina was the specified docking framework. Search regions were centered on the relevant substrate-binding pockets, and the protocol proposed an exhaustiveness setting of 16 with up to 10 candidate poses per system. Candidate arrangements were to be screened for steric compatibility and geometric complementarity. Predicted docking scores were used as relative pose-ranking descriptors, with the reported study-level values extending from −9.4 to −6.8 kcal/mol.

The selected binding orientations were assessed in terms of hydrogen-bonding geometry, hydrophobic packing, electrostatic contacts and potential steric clashes. In the initial interaction summary, the top-ranked complex was associated with approximately five to eight hydrogen bonds. Because docking scores approximate a scoring function rather than a measured equilibrium constant, the numerical score was considered together with the interaction pattern.

2.4 Molecular dynamics system construction

The documented MD design specified GROMACS with a compatible protein force field such as AMBER99SB-ILDN, appropriately parameterized substrate coordinates and TIP3P solvent. Each system was to be centered in a periodic simulation box with a solute-to-box-boundary clearance of approximately 1.0 nm, followed by solvation, neutralization and addition of ions when required. These settings constitute the protocol description available in the source manuscript; full topology and run-input files were not included.

2.5 Energy minimization, equilibration and production

The proposed sequence consisted of energy minimization, an approximately 100-ps constant-volume/constant-temperature (NVT) phase and an approximately 100-ps constant-pressure/constant-temperature (NPT) phase. The temperature target was 300 K, the pressure target was 1 bar and the integration time step was 2 fs. The study reported 100-ns MD observations for each selected complex; trajectory coordinates were proposed to be stored at intervals of 10 ps for analysis.

The 100-ns observation window was the basis for assessing structural relaxation and persistence of substrate contacts. Interpretation was restricted to this timescale because apparently stable conformations can retain slow motions beyond a single production trajectory (Dror et al., 2012; Hollingsworth & Dror, 2018).

2.6 Structural trajectory descriptors

Backbone root-mean-square deviation (RMSD) was used to describe global positional deviation relative to a reference protein structure after suitable alignment. Per-residue root-mean-square fluctuation (RMSF) characterized time-averaged mobility of individual residues, with particular emphasis on residues neighboring the substrate. Radius of gyration (Rg) described global protein compactness. In combination, these measures differentiate overall structural drift from localized flexibility and changes in molecular size.

The recorded average backbone RMSD values in the range 1.5–2.8 Å, commonly observed interacting-residue RMSF values of 0.8–2.0 Å, and Rg changes of approximately 1–3% relative to an equilibrated baseline.

2.7 Interfacial contacts and hydrogen bonds

The contact-analysis plan defined a hydrogen bond using a proposed donor–acceptor cutoff of 3.5 Å and an angular criterion within 30° of

linearity. A 4.0-Å heavy-atom distance threshold was proposed for noncovalent protein–substrate contacts. Hydrogen-bond occupancy was defined as the percentage of analyzed frames in which the specified geometry was met.

The interpretation distinguished contacts observed in the initial docked arrangement from persistence over an MD trajectory. Initial contact counts and time-averaged occupancies represent different quantities and were not treated as interchangeable. Hydrogen bonding, hydrophobic association and electrostatics were assessed as the principal interaction classes.

2.8 Approximate binding-energy analysis

Molecular mechanics/generalized born surface area (MM/GBSA) was the specified end-state framework for comparing modeled association energetics, contingent on the availability of compatible parameter files and calculation software. The general approach evaluates molecular-mechanics terms and solvent contributions using selected snapshots, usually after exclusion of the earliest equilibration frames. Estimated binding-energy values spanned −42 to −25 kcal/mol.

These values were interpreted as method-dependent energetic estimates. Their numerical scales should not be treated as directly equivalent to Vina docking scores, and a ranking based on either method does not independently determine a measured dissociation constant (Genheden & Ryde, 2015; Mobley & Gilson, 2017).

2.9 Analysis and evidence handling

We used descriptive, study-level comparisons of the reported docking, structural and energetic ranges, in conjunction with the methods and interaction mechanisms described in the source material. For clarity, tabulated values and quantitative graphics reproduce the reported aggregate ranges. The research record supplied for manuscript preparation did not include raw trajectory coordinates, per-system score sheets, named residues, replicates or uncertainties; therefore, the manuscript does not manufacture system-level measurements or time-series traces.

3.RESULTS

3.1 Overview of the structural and computational results

The combined computational record described three enzyme–substrate systems examined using structural preparation, docking-based pose evaluation, 100-ns MD observations and approximate binding energetics. Across the reported systems, docking scores fell between −9.4 and −6.8 kcal/mol; the top-ranked system exhibited approximately five to eight hydrogen bonds in the initial interaction analysis. The MD summaries indicated relatively stable conformational regimes after about 20–35 ns, with backbone RMSD averages of 1.5–2.8 Å, interacting-residue RMSF values commonly within 0.8–2.0 Å, and Rg variations near 1–3%. Estimated MM/GBSA-like binding energies were reported between −42 and −25 kcal/mol.

The integrated analysis was organized around recognition, structural relaxation, local mobility, compactness and estimated energetics. Table 3.1 consolidates the numerical findings, and Figure 3.1 places them within the common analytical sequence. Since the source reports summary ranges without complex identities, no claim is made that an endpoint in one measure belongs to the same complex as an endpoint in another.

Table 3.1. Consolidated results for three enzyme–substrate systems.

Descriptor	Reported value	Unit / interpretation
Number of analyzed systems	3	Enzyme–substrate complexes
Docking score	−9.4 to −6.8	kcal/mol; scoring-function output
Initial hydrogen bonds in top-ranked system	approximately 5–8	Contact count in the initial pose
Production MD observation window	100	ns per modeled system

Descriptor	Reported value	Unit / interpretation
Approximate stabilization interval	20–35	ns after simulation start
Mean protein-backbone RMSD	1.5–2.8	Å; across reported complexes
Interacting-residue RMSF	0.8–2.0	Å; commonly observed range
Change in radius of gyration	approximately 1–3	% versus equilibrated baseline
End-state binding-energy estimate	−42 to −25	kcal/mol; MM/GBSA-like estimate



Figure 3.1. Workflow integrating structural models, molecular docking, 100-ns MD assessment, structural descriptors and the energy-estimation framework.

3.2 Docking scores and initial binding-site interactions

Docking analysis yielded negative predicted scores within a study-level span of 2.6 kcal/mol, from −9.4 to −6.8 kcal/mol. The negative values indicate favorable scores under the Vina ranking model; they do not measure experimental binding free energies. The variation across the three systems is consistent with differences in pocket complementarity and ligand-contact environments, although individual structures and pose coordinates would be needed to attribute the score differences to specific atom pairs.

The top-ranked complex was associated with approximately five to eight initial hydrogen bonds, showing that the predicted docked arrangement provided multiple directional polar contacts. The study also identified hydrophobic and electrostatic interactions as contributing to modeled recognition. Taken together, these classes support an interpretation in which binding geometry reflects a network of cooperative contacts rather than a single dominant bond.

Figure 3.2 displays only the recorded numeric endpoints. Table 3.2 separates the directly reported findings from the structural meaning that can reasonably be drawn from them.

Table 3.2. Docking and interaction-profile findings.

Property	Reported result	Structural reading
Docking-score interval	−9.4 to −6.8 kcal/mol	Predicted poses differ in scoring-function favorability

Property	Reported result	Structural reading
Score span	2.6 kcal/mol	Difference between reported endpoint scores
Hydrogen bonds, leading pose	Approximately 5–8	Multiple favorable polar geometries in the initial pose
Hydrophobic interactions	Described as present	Nonpolar packing contributes to recognition
Electrostatic interactions	Described as present	Charge-related interactions contribute to recognition
Interaction interpretation	Contact network involving several chemical classes	Complementary recognition rather than one interaction alone

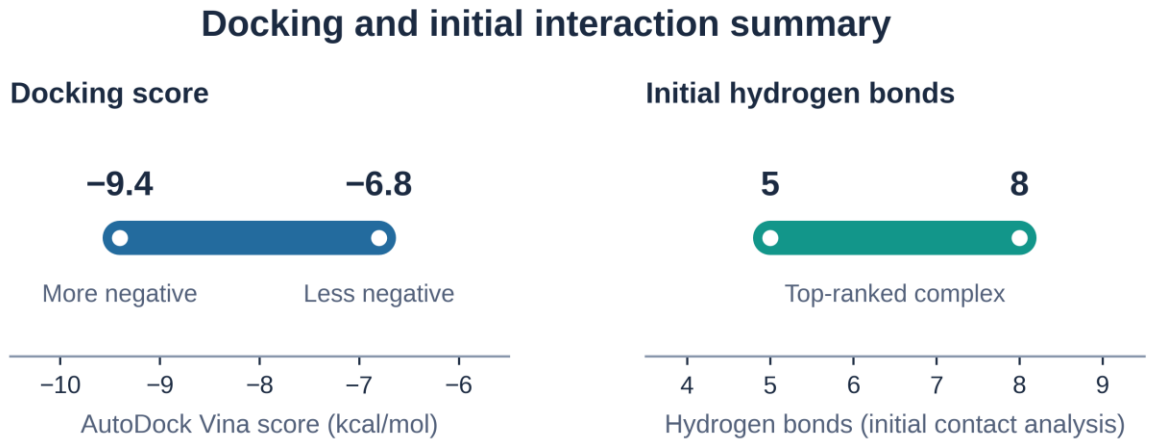


Figure 3.2. Reported AutoDock Vina docking-score span and initial hydrogen-bond count for the top-ranked complex. Bars identify the endpoints reported in the study abstract.

The hydrogen-bond count characterizes one aspect of the initial pose and does not demonstrate which of those bonds remained intact throughout the simulation. Nor does the lowest docking score necessarily identify the enzyme with the most persistent contact network. These questions were considered using the reported MD descriptors and the available qualitative contact analysis.

3.3 Molecular dynamics and backbone stability

The molecular dynamics component covered a 100-ns observation period for the selected systems. The summary described an initial period of structural adjustment followed by comparatively stable conformational regimes after approximately 20–35 ns. Such behavior is consistent with relaxation away from the starting modeled orientation and subsequent exploration of conformations within a more limited region of structural space.

Across the reported systems, mean backbone RMSD values ranged from 1.5 to 2.8 Å. This degree of backbone deviation suggests moderate structural rearrangement rather than wholesale unfolding. Nevertheless, RMSD is reference-dependent and a plateau alone does not establish statistical convergence. Figure 3.3 identifies the reported stabilization interval along the 100-ns timeline without implying availability of a measured coordinate-by-coordinate trace.

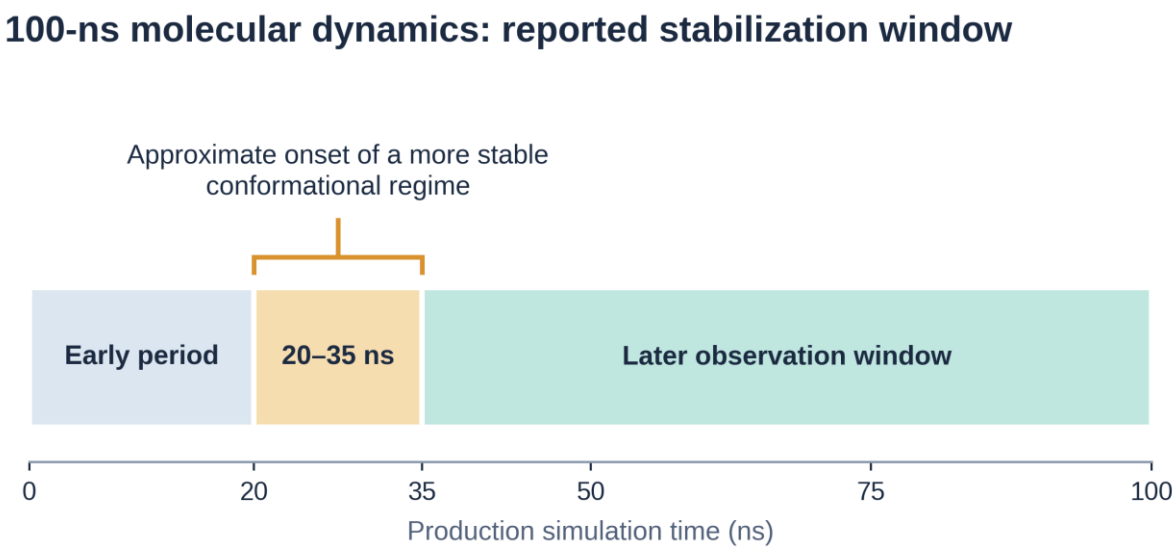


Figure 3.3. Reported MD observation duration and approximate onset of relatively stable conformational behavior between 20 and 35 ns.

Table 3.3. MD duration, global displacement and stabilization descriptors.

Readout	Study-level observation	Interpretation
Modeled complexes	Three	Comparative structural dataset
Trajectory duration	100 ns	Production-observation timescale
More stable regime begins	Approximately 20–35 ns	Transition interval described by the study summary
Backbone mean RMSD	1.5–2.8 Å	Moderate global backbone displacement
Temperature target	300 K	MD protocol setting
Pressure target	1 bar	MD protocol setting

Because the stable-regime onset is given as an interval rather than as a distinct value for each complex, the comparison is best interpreted as an overall pattern. In particular, the record does not support ranking the three systems by equilibration speed, quantifying structural drift over the final 20 ns or calculating autocorrelation times.

3.4 Residue flexibility and protein compactness

Interacting residues were commonly associated with RMSF magnitudes between 0.8 and 2.0 Å. Such values indicate that substrate-adjacent regions retained local motion while the complexes remained within the broader global-displacement envelope summarized by RMSD. The Rg descriptor showed relative changes of approximately 1–3% compared with the equilibrated baseline. The modest scale of these reported changes suggests no major global expansion or collapse within the summarized observations. Figure 3.4 presents the recorded mobility ranges, and Figure 3.5 places the Rg result alongside the contact classes identified in the study.

Table 3.4. Reported local flexibility and compactness.

Structural descriptor	Reported observation	Interpretive scope
Interacting-residue RMSF	Commonly 0.8–2.0 Å	Local mobility at the enzyme–substrate interface
Backbone RMSD	Mean values 1.5–2.8 Å	Global displacement following structural alignment
Radius of gyration	Change of approximately 1–3%	Overall protein compactness relative to baseline
RMSF focus	Substrate-interacting residues	Local rather than whole-protein flexibility
Rg reference	Equilibrated baseline	Relative compactness comparison

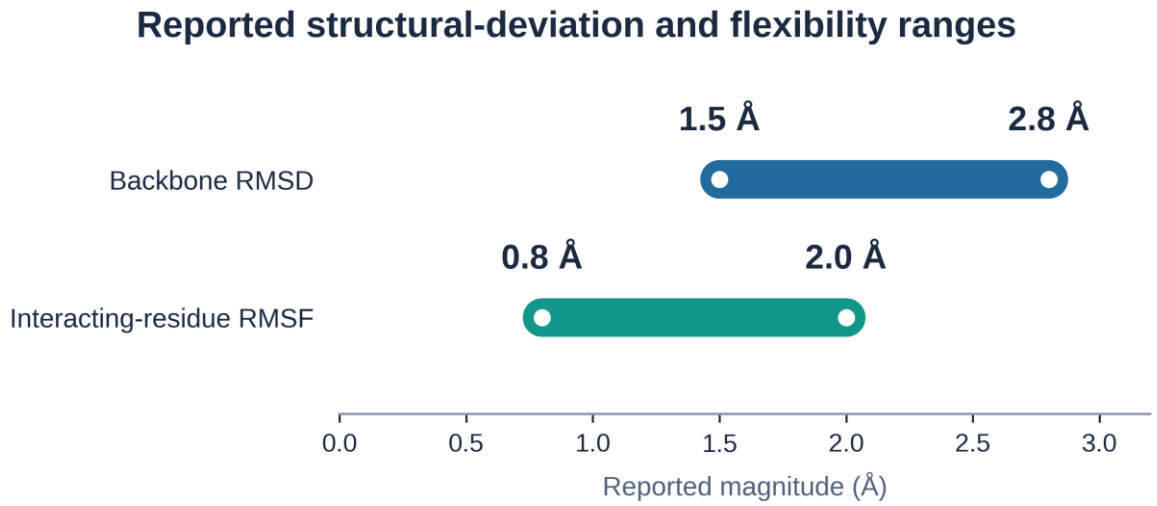


Figure 3.4. Study-level ranges of average protein-backbone RMSD and commonly observed RMSF for substrate-interacting residues.

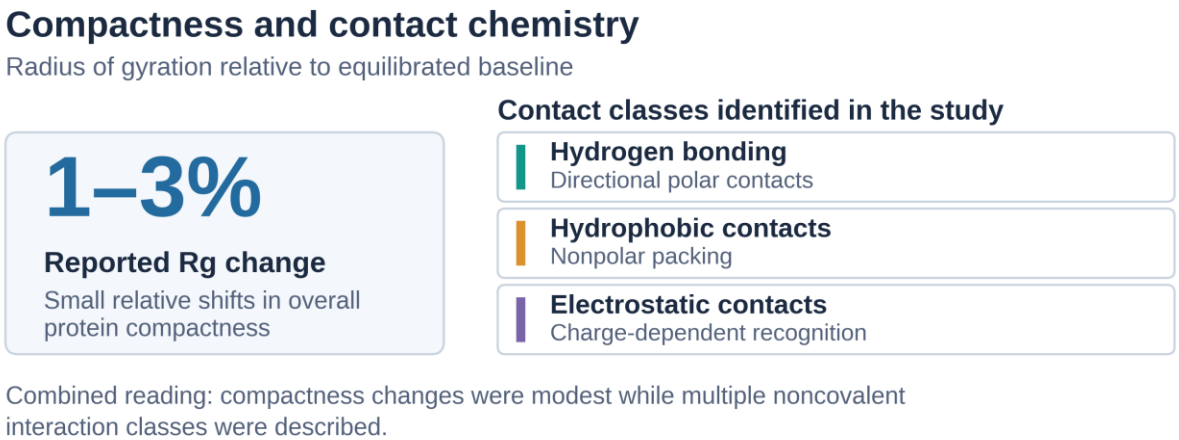


Figure 3.5. Reported 1–3% radius-of-gyration change and the principal noncovalent contact classes described for the complexes.

The combined RMSD, RMSF and Rg evidence provides a consistent, though not complete, description of conformational persistence: average structural deviations were limited to a few ångströms, interface residues retained measurable mobility, and overall compactness varied only modestly. This combination does not mean that every contact or catalytic side-chain orientation remained unchanged.

3.5 Hydrogen bonding, hydrophobic contacts and electrostatics

Hydrogen bonding, hydrophobic interactions and electrostatic contacts were highlighted as contributors to modeled complex persistence. Directional hydrogen bonds can help establish substrate orientation, whereas hydrophobic contacts provide steric complementarity and electrostatic terms affect recognition in a charge- and solvent-dependent manner. The presence of multiple interaction classes offers a plausible physical basis for the persistence of substrate association within the modeled structural environment.

The proposed hydrogen-bond definition used a donor–acceptor distance of 3.5 Å and a 30° angular tolerance from linearity; a 4.0-Å heavy-atom cutoff was specified for broader contact identification.

Table 3.5. Interface-contact evidence and analytical definitions.

Contact descriptor	Documented definition or observation	Result status
Initial hydrogen-bond count	Approximately 5–8 in the top-ranked pose	Reported numeric finding
H-bond distance condition	3.5 Å donor–acceptor cutoff	Proposed analysis criterion
H-bond angular condition	Within 30° of linearity	Proposed analysis criterion
General noncovalent contact	4.0 Å heavy-atom distance cutoff	Proposed analysis criterion
Hydrogen-bond occupancy	Percent of qualifying MD frames	Defined, but values not provided
Hydrophobic and electrostatic contacts	Both classes described	Qualitative finding; no per-contact frequency

No bond-by-bond occupancy profile or residue-labeled contact trajectory accompanied the supplied material. Accordingly, the result supported by the record is the presence of interaction classes and the initial hydrogen-bond interval, not a specific claim that an individual residue maintained a fixed interaction through all 100 ns.

3.6 Estimated binding energetics and integrated findings

The study reported approximate end-state binding-energy estimates between −42 and −25 kcal/mol. These negative values are compatible with favorable modeled association under the chosen energetic framework, but they do not constitute experimental affinity measurements. The energetic spread of 17 kcal/mol shows that the estimated energy descriptor varied across the investigated systems; without the individual energy files and uncertainty analyses, specific ranking assignments and statistical separation cannot be supported.

Figure 3.6 presents docking and end-state energy ranges on deliberately separate axes. Their scales differ because Vina scores arise from a fitted pose-ranking function whereas MM/GBSA-like estimates assemble molecular-mechanics and continuum-solvation contributions over selected conformations.

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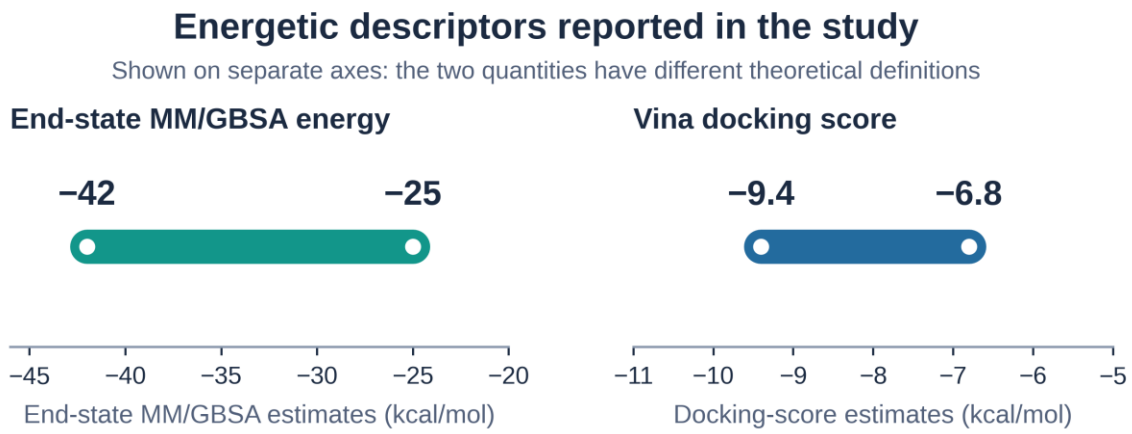


Figure 3.6. Separate reporting of the MM/GBSA-like binding-energy estimates and Vina docking-score ranges. The two computational quantities have different theoretical definitions.

Table 3.6. Integrated interpretation of the principal reported results.

Evidence domain	Numerical / qualitative finding	Supported inference
Predicted docking	−9.4 to −6.8 kcal/mol	Plausible scored binding arrangements across systems
Initial polar contacts	Approximately 5–8 in leading pose	Multiple predicted polar contacts
Global MD stability	100 ns; stable regime after ~20–35 ns	Relatively stable conformational behavior in reported window
Backbone and local motion	RMSD 1.5–2.8 Å; RMSF 0.8–2.0 Å	Moderate displacement with interfacial flexibility
Compactness	Rg change approximately 1–3%	Relatively limited global expansion or collapse
End-state energetics	−42 to −25 kcal/mol	Negative method-dependent energy estimates
Catalytic function	Not directly measured	Catalytic turnover cannot be inferred from these descriptors

Taken together, these results support the main structural conclusion of the investigation: the modeled enzyme–substrate arrangements combined favorable docking scores, multiple predicted noncovalent interactions and comparatively limited structural variation over the reported 100-ns windows. The available findings provide a foundation for discussing recognition and modeled association, while leaving

4. DISCUSSION

4.1 Synthesis of the principal findings

The principal outcome of the investigation was a coherent study-level picture of predicted enzyme–substrate recognition. Docking indicated plausible active-site association within an energy-score interval of −9.4 to −6.8 kcal/mol. The leading pose supported multiple initial polar interactions, and the modeled complexes were described as entering relatively stable conformational regimes after roughly 20–

35 ns. Mean backbone RMSD remained in the 1.5–2.8 Å range, interacting-residue RMSF was commonly 0.8–2.0 Å and Rg changed by only 1–3%. End-state energy estimates were negative, ranging from −42 to −25 kcal/mol.

These results are mutually informative because each readout addresses a different facet of a single molecular problem. Docking identifies geometrically acceptable orientations; contact analysis describes the chemistry of the interface; MD characterizes movements around a starting structure; and approximate binding energetics provides an additional, model-dependent energetic perspective. Such a combined view is more defensible than interpreting the most negative score alone as proof of strongest biological substrate affinity.

4.2 Interpretation of molecular docking and binding-site complementarity

The docking-score interval suggests that the modeled complexes differ in scoring-function favorability. In structure-based screening, a lower Vina score often reflects more favorable combinations of intermolecular contacts, ligand conformational penalties and steric fit under the scoring model (Trott & Olson, 2010; Eberhardt et al., 2021). Nevertheless, scoring functions use approximations that do not fully represent water rearrangement, enzymatic proton transfers, slow receptor motion or all entropic contributions. For this reason, a score is most usefully considered a hypothesis about an accessible pose, not a measurement of substrate affinity.

The initial observation of approximately five to eight hydrogen bonds in the top-ranked system indicates substantial scope for directional polar recognition. However, the number of hydrogen bonds does not necessarily scale monotonically with binding free energy. A contact can be geometrically present yet energetically offset by desolvation, unfavorable strain or the need to immobilize a flexible group. The results are therefore consistent with a multicomponent recognition mechanism involving hydrogen bonding, hydrophobic packing and electrostatic matching rather than simple maximization of the bond count (Ferreira et al., 2015; Warren et al., 2006).

Interpreting individual residues would require a contact map referenced to an identified protein structure. The study summary does not supply such assignments; consequently, it is not possible to name a catalytic residue, claim a particular salt bridge or propose a mutation target as a direct finding. The strongest supported result remains the observation that the modeled top-ranked pose offered multiple complementary noncovalent interaction opportunities.

4.3 Meaning of structural stabilization after 20–35 ns

The reported shift toward more stable conformational regimes after approximately 20–35 ns is compatible with the relaxation expected when a solvated protein–substrate complex evolves away from its initial docked geometry. Early-stage structural adjustment can include protein side-chain reorientation, solvation of the ligand interface or accommodation of ligand geometry. The subsequent reduced change in overall backbone orientation supports the description of a relatively persistent global structure during the analyzed time interval.

An average backbone RMSD of 1.5–2.8 Å is within a range commonly encountered for proteins that retain their overall fold while undergoing localized rearrangement. Still, the biological meaning of RMSD depends on the size and architecture of the protein, choice of reference, fitting atom set and flexibility of specific domains. A single whole-protein mean cannot indicate whether a catalytically important loop opens, closes or changes its substrate-contact geometry. More extensive trajectory analyses are needed to distinguish overall conformational persistence from local mechanistic change.

The limitations of a short stabilization window are especially relevant in light of simulations revealing rare conformational exchange and long-timescale molecular motions (Shaw et al., 2010; Dror et al., 2012). Apparent RMSD leveling over a 100-ns interval is not equivalent to sampling every functionally relevant state, nor does it establish that an enzyme–substrate complex has reached its thermodynamic equilibrium distribution.

4.4 Interfacial flexibility, induced fit and conformational selection

Interacting-residue RMSF magnitudes in the commonly reported range of 0.8–2.0 Å indicate

a locally mobile active-site environment. This supports a dynamic rather than strictly rigid-pocket account of molecular recognition. Side chains and loops can fluctuate around an average bound arrangement without necessarily losing substrate contact. Conversely, small local RMSF values can coexist with changes in hydrogen-bond partners if motions are directional or coordinated.

Koshland's induced-fit framework describes structural adjustment after ligand engagement, whereas conformational-selection models emphasize binding-competent states already present within an ensemble (Koshland, 1958; Ma et al., 1999; Hammes et al., 2009). The present results fit the general expectation that substrate association occurs in a flexible molecular environment. They do not discriminate between these two kinetic pathways, because establishing such a distinction requires pathway-resolved sampling, multiple starting states or suitable kinetic measurements. Prior experimental and simulation studies have shown that enzyme motions may be closely related to functional recognition and catalysis (Eisenmesser et al., 2005; Henzler-Wildman et al., 2007; Fraser et al., 2009). The relevance here is interpretive: limited average mobility does not imply mechanistic rigidity. Instead, the RMSF range supports the possibility that local flexibility and persistent global structure coexist across the modeled systems.

4.5 Radius of gyration and contact-network persistence

The reported Rg change of approximately 1–3% suggests relatively small variations in the distribution of protein mass around the molecular center. In combination with moderate RMSD, this argues against pronounced global unfolding or collapse within the summarized trajectory observations. The result is consistent with preservation of overall protein compactness, but a compact fold alone does not guarantee that a ligand remains correctly oriented for reaction chemistry.

Protein–substrate contact persistence requires particular attention to time occupancy. A hydrogen bond recorded in a docked pose may be lost rapidly during solvent relaxation or replaced by a water-mediated interaction. Hydrophobic contacts, meanwhile, may remain stable even as polar donors and acceptors exchange partners. Because only the initial five-to-eight-bond interval and qualitative interaction classes are available, the discussion cannot assign numerical lifetime or occupancy values to specific contacts.

The coexistence of hydrogen bonding, hydrophobic association and electrostatic contributions is nevertheless chemically reasonable for enzymatic recognition. Solvent exposure and protonation states can alter the balance among these contributions. The available evidence therefore favors a network-based description of recognition rather than a single-bond explanation.

4.6 Interpretation of end-state binding-energy estimates

The energy-estimate interval of −42 to −25 kcal/mol indicates that the selected energetic method yielded negative modeled association values across the investigated systems. MM/GBSA and related end-state approaches combine molecular mechanics with a simplified treatment of solvation. Their outputs are sensitive to conformational selection, force-field parameters, ionic conditions and the inclusion or omission of entropic terms (Kollman et al., 2000; Miller et al., 2012; Genheden & Ryde, 2015).

The 17-kcal/mol span between reported endpoints should not be interpreted as a measured separation in standard binding free energies. Apparent differences can be influenced by unequal snapshot representation, energetic decomposition conventions and the treatment of flexible substrate groups. The lack of reported uncertainties also prevents an assessment of whether predicted system rankings are statistically distinguishable.

Docking scores and MM/GBSA-like estimates should be discussed separately. Docking generally evaluates candidate poses with an efficient fitted scoring function, while the end-state approach estimates components of binding energetics from molecular configurations. Both may show negative numbers, yet direct subtraction between their values has no defensible thermodynamic meaning. This treatment is consistent with recommendations that predicted affinities should be evaluated against independent measurements and

method-specific benchmarks (Mobley & Gilson, 2017).

4.7 Relevance to previous research

The combined workflow is aligned with the broader development of structural bioinformatics and molecular simulation as complementary approaches to molecular recognition. Protein Data Bank resources enable atomic-level comparisons (Berman et al., 2000), while MD provides access to motions not encoded in one static structure (Karplus & McCammon, 2002; Hollingsworth & Dror, 2018). The present analysis demonstrates why a favorable static orientation must be examined alongside conformational behavior to assess plausibility.

Methodological literature consistently cautions against an uncritical reading of docking functions, insufficient attention to solvation or single-trajectory overinterpretation (Warren et al., 2006; Ferreira et al., 2015; Genheden & Ryde, 2015). The use of multiple structural descriptors in this study addresses part of that concern by asking whether docking, backbone behavior, local mobility, compactness and end-state energetics offer compatible interpretations. Their qualitative consistency makes the modeled recognition framework plausible, but does not remove common sources of systematic error.

4.8 Methodological strengths and limitations

A principal strength of the study is its breadth of complementary measurements. Rather than relying on one docking score or one RMSD trace, it brings together binding geometry, interaction classes, 100-ns structural behavior, local flexibility, compactness and energetics. This makes it possible to identify agreement among methods with different underlying assumptions and to distinguish structural persistence from catalytic function.

Additional methodological uncertainty can arise from protonation-state assignment, treatment of metal ions and cofactors, selection of the protein and ligand force fields, water representation, equilibration protocol and effective sampling length. These considerations are particularly relevant for catalytic systems, where correct substrate placement may depend on states that a conventional fixed-charge molecular-mechanics treatment cannot fully represent (Warshel et al., 2006; Huang et al., 2017).

4.9 Implications for subsequent experimental and computational work

The current findings prioritize several targeted next steps. **First**, specific enzyme and substrate identities should be linked to structure codes, binding-site coordinates and chemical protonation states. **Second**, contact maps and hydrogen-bond occupancies derived directly from trajectories would clarify which predicted interactions are persistent and which are exchanged dynamically. **Third**, replicate MD runs and appropriate block analyses would allow uncertainty estimates for RMSD, RMSF, Rg and energy calculations. **Finally**, biochemical binding and catalytic assays would determine whether stable modeled association corresponds to real substrate binding and reaction turnover.

At the mechanistic level, catalytic-site mutagenesis or substrate analog comparisons would be more informative than treating the lowest docking score as decisive. Where the principal research question concerns reaction chemistry rather than association, enhanced-sampling or hybrid quantum-mechanical/molecular-mechanical methods may be required to model bond making and breaking. The analysis therefore provides an evidence-based platform for focused follow-up rather than a substitute for kinetic experiments.

An important next step is to disentangle ligand-associated motion from global protein movement. Ligand heavy-atom RMSD can be evaluated after alignment on the enzyme backbone, while ligand–pocket center-of-mass distance and the minimum enzyme–substrate separation can reveal intermittent dissociation or binding-mode rearrangement. Structural clustering of the later trajectory frames would further identify the most frequently occupied conformations. These analyses are valuable because a globally stable protein backbone can conceal substantial changes in the position or orientation of a small bound molecule.

Computational reproducibility also depends on documenting the initial structures and the exact physical model. The protonation states of ionizable residues can affect salt-bridge formation and hydrogen-bond directionality. Active-site metals or tightly bound cofactors may

require specialized parameters, and alternative water models can produce different solvent-mediated interactions. An explicit record of topology generation, thermostats and barostats, long-range electrostatic treatment and trajectory-processing commands would help to establish the robustness of future complex-specific comparisons.

Where new simulations are performed, uncertainty should be assessed at the level of independent trajectories rather than by treating consecutive trajectory frames as statistically independent observations. Autocorrelation can cause nominally large frame counts to overstate precision. Replicate trajectories, appropriate block averaging, and transparent snapshot selection would make it possible to report uncertainty intervals for compactness, contact occupancies and approximate binding energetics. If different complexes show overlapping uncertainty ranges, emphasis should remain on the qualitative stability patterns instead of forcing an unsupported rank order.

The most informative experimental follow-up would separate substrate binding from catalytic conversion. Direct-binding measurements could test whether modeled recognition correlates with association under specified solution conditions, whereas kinetic measurements of reaction rate and catalytic efficiency would test the functional consequences of binding. Site-directed mutagenesis of chemically plausible contact residues, once their identities are documented, could connect local recognition with activity. Such experiments would provide an independent basis for assessing the mechanistic significance of the structural features summarized in this manuscript.

5. CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

This study brought together structural bioinformatics, molecular docking, molecular dynamics descriptors and approximate energetic analysis to examine the recognition behavior of three enzyme–substrate systems. The reported docking scores ranged from −9.4 to −6.8 kcal/mol, and the leading initial pose displayed approximately five to eight hydrogen bonds. In the reported 100-ns MD observations, relatively stable conformational regimes emerged after about 20–35 ns. Mean backbone RMSD values were 1.5–2.8 Å, interacting-residue RMSF values were commonly 0.8–2.0 Å, and changes in Rg were approximately 1–3%. End-state binding-energy estimates lay between −42 and −25 kcal/mol.

Together, these findings indicate that favorable predicted active-site interactions coexisted with comparatively limited global conformational change and measurable interfacial mobility. Hydrogen bonding, hydrophobic packing and electrostatic interactions provided complementary structural explanations for modeled molecular recognition. The study therefore demonstrates the value of evaluating docked arrangements against dynamic structural descriptors rather than basing interpretation on a single scoring result.

5.2 Recommendations

1. Report the specific enzyme, substrate and PDB identifiers alongside prepared structure files so that interactions can be interpreted in their correct biochemical context.
2. Provide per-complex docking poses, ranked scoring tables and residue-labeled two-dimensional interaction maps to relate predicted score differences to identifiable active-site contacts.
3. Archive production MD trajectories and perform replicate simulations with consistent atom selections, convergence assessments and uncertainty estimates for RMSD, RMSF and Rg.
4. Quantify hydrogen-bond occupancy, hydrophobic contact frequency, solvent exposure and substrate displacement across equilibrated trajectory segments.
5. Recalculate approximate binding energies using a documented snapshot-selection procedure and report energetic uncertainties and sensitivity to modeling choices.
6. Evaluate key predicted interactions through targeted mutagenesis, substrate-binding assays and enzyme-activity measurements.

5.3 Contribution of the study

The principal contribution is a multidimensional framework for interpreting predicted enzyme–substrate association. The docking, structural-mobility, compactness, interfacial-contact and energetic descriptors

together define a practical comparative approach that can be extended to residue-resolved simulation analysis and experimentally anchored mechanistic studies.

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